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Review Article

Pharmacogenomics of Leukemia: Unlocking Personalized Treatment Strategies

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Abstract

Leukemia, a diverse group of blood cancers, continues to present significant challenges in diagnosis, and treatment. Recent advancements in pharmacogenomics have opened new avenues for therapeutic strategies tailored to the unique genetic and molecular characteristics of each individual patient. In leukemia, genetic polymorphisms have been revealed that influence drug metabolism, efficacy, and the risk of adverse effects. Notable examples include *TPMT* variants affecting thiopurine treatment in Acute Lymphoblastic Leukemia (ALL) and *UGT1A1* polymorphisms impacting irinotecan toxicity in Acute Myeloid Leukemia (AML). Additionally, *SLCO1B1* variants influence methotrexate response in ALL. Targeted therapies have revolutionized leukemia treatment, focusing on specific genetic abnormalities. Tyrosine kinase inhibitors (TKIs), like imatinib, have successfully treated Chronic Myeloid Leukemia (CML) with the *BCR-ABL* fusion gene. Similarly, immunotherapies, such as CAR T-cell therapy, have reshaped treatment paradigms for B-cell ALL. The personalized approach minimizes adverse effects while optimizing treatment efficacy. Moreover, genetic markers are aiding in the identification of patients at higher risk of developing cardiotoxicity from anthracycline chemotherapy. This article provides an overview of the evolving landscape of pharmacogenomics in leukemia, highlighting key findings and trends. Furthermore, combinatorial therapies, biomarker discovery, and patient-centric care are expected to enhance treatment outcomes and survivorship.

Keywords: Acute lymphoblastic leukemia, immunotherapies, genetic polymorphisms, pharmacogenomics, adverse effects, efficacy

1. Introduction

Leukemia is a cancer that originates in the bone marrow, affecting the blood and blood-forming tissues. It is characterized by the uncontrolled proliferation of abnormal white blood cells, which are essential for the body's immune system and fighting infections (Hallek 2019). These abnormal white blood cells, known as leukemia cells, do not function properly and crowd out healthy blood cells, leading to weakened immunity and various health problems. Leukemia can be acute (progressing rapidly) or chronic (developing more slowly). It is categorized into different types based on the specific type of white blood cell affected, in addition to other factors. The treatment and prognosis for leukemia depend on its type, stage, and the patient's health (Lee et al. 2020).

2. Epidemiology of Leukemia

Leukemia is a relatively less common cancer compared to some other types, but it still affects a significant number of children and adults. The incidence rate varies by age, with different types of leukemia having other age distributions (Lee et al. 2020, Li et al. 2020). According to the Global Cancer Incidence, Mortality and Prevalence Project (GLOBOCAN) 2020, Leukemia is listed

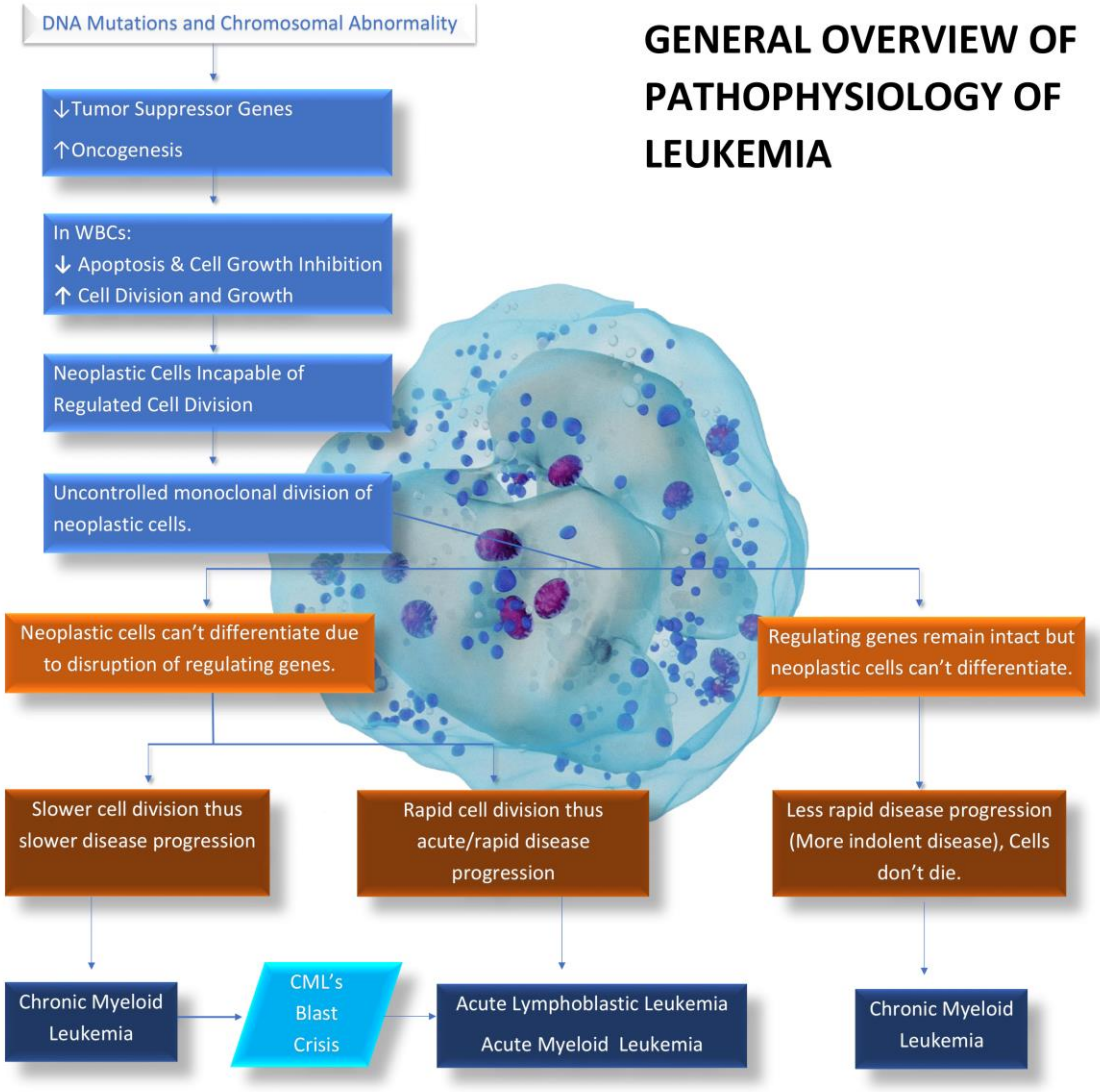

Figure 1: Leukemia Pathophysiology Overview.

as the 11th leading cause of death, globally, and the 15th most commonly diagnosed cancer. It is more prevalent among males than females. The mortality rate is also higher among males, as compared to females (Sung et al. 2021). Moreover, according to the Global Burden of Disease, cases of leukemia increased by 26% from 2005 to 2015 (Ou et al. 2020). Acute Lymphoblastic Leukemia (ALL) is more common in children, while Acute Myeloid Leukemia (AML), and Chronic Lymphocytic Leukemia (CLL) are more common in older adults. The incidence of leukemia varies worldwide. It tends to be more common in the western countries than in the developing regions. However, this pattern may change due to genetics, environmental exposures, and healthcare infrastructure (Landau et al. 2015).

3. Risk Factors for Developing Leukemia

Some genetic syndromes, such as Down syndrome and specific inherited genetic mutations, can increase the risk of leukemia. Exposure to high levels of ionizing radiation,

such as in atomic bomb survivors or nuclear accidents, is a known risk factor. Long-term exposure to certain chemicals, like benzene, is associated with a predisposition to leukemia (Brüggemann et al. 2009). Some cancer treatments, particularly radiation therapy and certain chemotherapy drugs, may elevate the risk of developing secondary leukemia. Similarly, certain viruses, like the human T-cell lymphotropic virus (HTLV-1), and some retroviruses, have been linked to the development of specific types of leukemia. Leukemia affects males and females, but the incidence can vary by gender for specific types (Wyatt and Bram 2019). For example, AML is slightly more common in men, while CLL is more common in women. As mentioned earlier, age is a significant factor, and different types of leukemia are more prevalent at different stages of life. Survival rates for leukemia have improved over the years due to advances in diagnosis and treatment. The prognosis varies, depending on factors such as the type of leukemia, age at diagnosis, stage, and response to treatment (Lee and Yang 2017). Some forms of leukemia are treatable, and have high survival rates, while others can be more aggressive and have lower survival rates. Prevention efforts often focus on avoiding known risk factors like exposure to carcinogens (e.g., benzene), maintaining a healthy lifestyle, and genetic counseling for individuals with a family history of leukemia or genetic predispositions (Bárcenas-López et al. 2021).

4. Current Treatment Approaches

The treatment regimen for leukemia varies depending on the type of leukemia, its subtype, the patient's age, overall health, and other individual factors. Treatment for leukemia typically involves a combination of therapies, including chemotherapy, radiation therapy, targeted therapies, stem cell transplantation (also known as bone marrow transplantation), and immunotherapy (Lee and Yang 2017, Bárcenas-López et al. 2021, Ansari et al. 2009). The following is a general overview of the current treatment approaches for the major types of leukemia:

4.1. **Chemotherapy:** The backbone of treatment is intensive chemotherapy. Different phases of chemotherapy are used to induce remission, consolidate, and maintain it, by using drugs like fludarabine, and Cyclophosphamide.

4.2. **CNS Prophylaxis:** To prevent leukemia cells from spreading to the central nervous system (CNS), intrathecal chemotherapy and/or cranial irradiation may be used (Landau et al. 2015).

4.3. **Targeted Therapy:** In some cases, targeted therapies like monoclonal antibodies (e.g. rituximab), *FLT3* inhibitors or *IDH* inhibitors, Tyrosine Kinase Inhibitors (TKIs) like ibrutinib, venetoclax, and obinutuzumab are used to target and kill leukemia cells specifically (Li et al. 2020).

4.4. **Stem Cell Transplantation:** Allogeneic stem cell transplantation (often from a matched donor) may be considered for high-risk or relapsed cases.

4.5. **Consolidation Therapy:** Additional chemotherapy or stem cell transplantation is used to consolidate the remission (Li et al. 2020).

4.6. **Supportive Care:** In all types of leukemia, supportive care is an integral part of treatment. This includes managing the side effects of treatment, such as infection prevention and control, blood transfusions, and supportive medications (Landau et al. 2015).

4.7. **Immunotherapy:** In recent years, immunotherapy approaches, such as chimeric antigen receptor (CAR) T-cell therapy, have shown promise in treating some types of leukemia, especially relapsed or refractory B-cell ALL.

5. Variability in Treatment Response

Inter- and intraindividual variability in leukemia patients is a complex yet common phenomenon. Several factors contribute to this variation, making it challenging for healthcare providers to predict an individual's treatment response (Sattarzadeh Bardsiri et al. 2022, Sharifi et al. 2014). Some of the key factors that influence the variability in treatment response for leukemia include:

Different types and subtypes of leukemia have distinct characteristics, and genetic mutations that can affect treatment response. For example, ALL and AML have different treatment approaches and outcomes (Wyatt and Bram 2019, Lee and Yang 2017). Specific genetic mutations and chromosomal abnormalities within leukemia cells can significantly impact treatment response. Certain modifications may make leukemia cells more or less susceptible to particular therapies. For example, the presence of the Philadelphia chromosome in CML is associated with a better response to TKIs. Moreover, age can influence both the treatment approach and response. Children and adults may receive different treatments; outcomes can vary based on age. A patient's overall health and other medical conditions can affect treatment response. Patients with compromised immune systems or preexisting health issues may have different outcomes (Ansari et al. 2009, Puente et al. 2015, Quiroz et al. 2019, Coccaro et al. 2019).

Patients who have received previous treatments, such as radiation or chemotherapy for other cancers, may have different responses to subsequent leukemia treatments. Over time, leukemia cells can potentially develop resistance to specific drugs, leading to treatment failure, primarily due to genetic changes in leukemia cells (Brüggemann et al. 2009). A patient's adherence to regimens, including taking medications, as prescribed, and attending follow-up appointments, is critical for treatment success. On the other hand, non-adherence can result in poor outcomes. Additionally, genetic variations in drug-metabolizing enzymes and drug transporters can influence how individuals metabolize and respond to chemotherapy drugs (Wyatt and Bram 2019). Pharmacogenomic testing can help identify these variations and guide treatment decisions, selecting the most appropriate drugs and dosages for each patient, and treatment monitoring, ultimately improving treatment outcomes and minimizing the risk of adverse effects. Adequate supportive care, including infection prevention, blood transfusions, and management of treatment-related side effects, can impact a patient's ability to tolerate anti-cancer therapy and respond effectively (Quiroz et al. 2019, Coccaro et al. 2019).

6. Genetic Polymorphism

It plays a significant role in leukemia treatment, genetic variations among patients can impact drug metabolism, drug efficacy, treatment response, and the risk of adverse effects (Frikha 2020). Provided below are some key ways in which genetic polymorphism is relevant in leukemia treatment:

Genetic variations in CYP3A4 and CYP3A5 enzymes can influence the metabolism of drugs like imatinib, dasatinib, and vincristine, commonly used in leukemia treatment (Yang et al. 2014). Individuals with certain variants may metabolize these drugs more rapidly or slowly, influencing their effectiveness and potential side effects. Genetic polymorphisms in drug transporters, such as ATP-binding cassette (ABC) transporters, can impact the uptake and efflux of chemotherapy drugs within cells (Coccaro et al. 2019), altering the drug concentrations inside cancer cells, and affecting the drug response. The ABC transporter ABCB1, also known as P-glycoprotein, is involved in transporting several chemotherapy drugs (Wyatt and Bram 2019). Polymorphisms in the *ABCB1* gene can influence the drug efflux and treatment response.

Moreover, genetic polymorphisms can also influence an individual's susceptibility to

Table 1. Summary of genes involved in the pharmacogenomics of leukemia and associated drugs.

Gene	SNPs	Sample Size	Population	Drugs	Disease	Association	References
TPMT	rs1800460	630	European	Thiopurines (e.g., mercaptopurine, thioguanine)	Thiopurine Toxicity	Strongly associated with toxicity.	(Almoguera et al. 2014)
	rs1142345	630	European				(Almoguera et al. 2014)
	rs1800462	250	Bangladesh				(Rashid et al. 2020)
UGT1A1	rs8175347	455	Spanish	Irinotecan	Irinotecan-induced toxicity	Associated with toxicity	(Díaz-Santa et al. 2020)
ABCB1 (MDR1)	rs1045642	51	American	Various chemotherapy drugs	Various cancers	Associated with response to drugs	(Yunis et al. 2023)
SLCO1B1	rs10841753	355	Chinese	Methotrexate	ALL	Associated with toxicity.	(Liu et al. 2017)

adverse effects related to drug treatment. For example, some genetic variants may predispose a patient to chemotherapy-induced toxicity, such as myelosuppression (reduced blood cell counts), hepatotoxicity (liver damage), or cardiotoxicity (heart damage).

Advances in understanding leukemia's genetic and molecular basis have led to the development of targeted therapies. These drugs are designed to specifically target cancer cells with specific genetic abnormalities while sparing healthy cells. TKIs, like imatinib, are quite effective in treating CML with the *BCR-ABL* fusion gene (Quiroz et al. 2019). Genetic polymorphisms can contribute to the development of drug resistance in leukemia. Mutations in specific genes may confer resistance to chemotherapy drugs, making it challenging to achieve remission. Identifying these mutations through genetic testing can guide treatment decisions and the selection of alternative therapies (Wahlund et al. 2020).

7. Pharmacogenetic Studies on Treatment Response in Leukemia

Numerous studies have investigated how specific genetic variations may influence the response of leukemia patients to various treatments (Ansari et al. 2009). These studies often focus on identifying genetic markers that can predict treatment outcomes, guide treatment decisions, and optimize therapeutic approaches. These studies were conducted in Canada and various Asian and European countries. Although genetic polymorphism in many genes was found to affect the treatment response in leukemia, *TPMT*, *SLC29A1,* and *BCR-ABL* fusion genes were found to have significant associations with treatment response. Below are some examples of key findings and studies in this area:

7.1. *TPMT* Genetic Variants and Thiopurine Treatment Response

Thiopurine drugs (e.g., mercaptopurine) are commonly used to treat ALL. Genetic variations in the *TPMT* gene have been well-studied and are known to impact thiopurine metabolism. Individuals with certain *TPMT* polymorphisms risk developing severe myelosuppression (low blood cell counts) when treated with standard doses of thiopurines. Pharmacogenetic testing for *TPMT* variants is routinely used to guide thiopurine dosing to avoid toxicity (Puente et al. 2015).

7.2. *BCR-ABL* Mutations and TKI Response in CML

The presence of the *BCR-ABL* fusion gene represents CML; mutations in this gene can lead to TKI resistance. Understanding the genetic profile of *BCR-ABL* mutations can help select the most appropriate TKI for individual patients (Yang et al. 2014).

7.3. Nucleoside Transporter Polymorphisms and Response to Fludarabine in CLL

Fludarabine is used in the treatment of CLL. Genetic variations in nucleoside transporter genes (e.g., *SLC29A1*) have been associated with differences in CLL's fludarabine uptake and treatment response. Studies have explored the relationship between these genetic polymorphisms and fludarabine efficacy (Frikha 2020).

7.4. Genetic Variants and Anthracycline-Induced Cardiotoxicity

Anthracycline chemotherapy drugs (e.g., doxorubicin) can cause cardiotoxicity in leukemia patients. Some genetic polymorphisms, including those in genes related to cardiac function, may increase the risk of anthracycline-induced cardiotoxicity (Quiroz et al. 2019).

7.5. Pharmacogenomic Profiling in Pediatric ALL

Several studies have explored the utility of comprehensive pharmacogenomic profiling in pediatric patients diagnosed with ALL. These studies aim to identify genetic markers that can guide treatment decisions, predict response to specific chemotherapy drugs, and reduce the risk of adverse effects (Sharifi et al. 2014).

7.6. Genomic Profiling for Targeted Therapies

Advances in genomic sequencing techniques have identified specific genetic alterations driving leukemia. Targeted therapies are being developed to match these genetic abnormalities, improving treatment outcomes, and reducing side effects.

8. Studies on the Association of Genetic Polymorphism with Adverse Effects on Leukemia

Research on the association of genetic polymorphisms with adverse effects in the treatment of leukemia is essential for personalized medicine. Understanding how genetic variations influence a patient's susceptibility to treatment-related side effects can help healthcare providers make more informed treatment decisions and minimize potential harm (Al-Absi et al. 2017, Sattarzadeh Bardsiri et al. 2022). Here are some examples of studies and findings related to the association between genetic polymorphism and adverse effects in the treatment of leukemia:

8.1. *TPMT* Genetic Variants and Thiopurine-Induced Myelosuppression

As mentioned previously, several studies have shown a strong association between genetic variations in the *TPMT* (thiopurine S-methyltransferase) gene and thiopurine-induced myelosuppression, which is a significant adverse effect of drugs like mercaptopurine and thioguanine used in the treatment of ALL. Patients with certain *TPMT* polymorphisms are at higher risk of developing severe myelosuppression, and pharmacogenetic testing for *TPMT* variants is now a standard practice to guide dosing adjustments to reduce this risk (Coccaro et al. 2019, Yang et al. 2014).

8.2. *UGT1A1* Polymorphisms and Irinotecan Toxicity in AML

Irinotecan is a chemotherapy drug used to treat AML. Genetic polymorphisms in the *UGT1A1* gene have been associated with an increased risk of irinotecan-induced toxicities, such as neutropenia and diarrhea. Research has shown that patients with specific *UGT1A1* variants are more susceptible to these adverse effects, prompting clinicians to consider dose adjustments (Coccaro et al. 2019).

8.3. *ABCB1* Genetic Variations and Chemotherapy Toxicity

The *ABCB1* gene encodes the P-glycoprotein transporter, which plays a role in drug efflux from cells. Genetic polymorphisms in *ABCB1* have been studied in various leukemia treatment settings. Some studies have suggested that certain *ABCB1* variants may be associated with an increased risk of chemotherapy toxicity, including myelosuppression, and gastrointestinal side effects (Sazawal et al. 2014).

8.4. *SLCO1B1* Polymorphisms and Methotrexate Toxicity in ALL

Methotrexate is a common chemotherapy drug used to treat ALL. Polymorphisms in the *SLCO1B1* gene, which is involved in drug transport, have been investigated concerning methotrexate toxicity. Some research has indicated that specific *SLCO1B1* genetic variants may influence the risk of methotrexate-related toxicities, such as mucositis, and hepatotoxicity (Frikha 2020).

8.5. Pharmacogenetic Profiling for Minimizing Adverse Effects

Comprehensive pharmacogenetic profiling is being explored to identify genetic markers associated with various adverse effects in the treatment of leukemia. These profiles may help clinicians tailor treatment regimens and supportive care strategies to minimize adverse effects while maintaining treatment efficacy (Bárcenas-López et al. 2021).

9. Recommendation and Future Perspectives

The future of leukemia treatments holds promise, driven by ongoing research and advancements in understanding the disease, as well as innovations in medical technology and therapeutics (Wyatt and Bram 2019). Personalized medicine will continue to play a significant role in leukemia treatment. Advances in genomics and molecular profiling will enable the identification of specific genetic mutations, and abnormalities driving leukemia (Coccaro et al. 2019). Targeted therapies designed to attack these genetic vulnerabilities will become more robust, improving outcomes with fewer side effects. Immunotherapy approaches, such as CAR T-cell therapy, will continue to evolve, as researchers are working on expanding the use of CAR T-cell therapy beyond B-cell ALL to other types of leukemia, including AML, and CLL. Additionally, combination therapies that integrate immunotherapy with other treatments will also be explored (Quiroz et al. 2019, Coccaro et al. 2019, Wahlund et al. 2020).

The development of small molecule inhibitors that target various signaling pathways within leukemia cells will continue to expand. These inhibitors can offer alternative therapeutic options for patients, especially for those who do not respond well to standard therapies or have relapsed (Brüggemann et al. 2009). Gene editing technologies, such as CRISPR-Cas9, can potentially correct genetic abnormalities that drive leukemia. While this area is still in the early stages of research, it offers exciting prospects for precision medicine in the treatment of leukemia. Natural killer (NK) cells are another type of immune cell that can be engineered to target leukemia cells. CAR-NK cell therapy is being explored as a potential treatment approach, which may offer advantages in terms of safety and broader applicability (Coccaro et al. 2019).

Ongoing research into leukemia biomarkers will enable early diagnosis, monitoring of treatment response, and identifying potential relapses. Liquid biopsies that analyze circulating tumor DNA (ctDNA) will become increasingly important. The development of novel combinations of drugs, including targeted therapies, immunotherapies, and conventional chemotherapy, will continue. Combinatorial approaches can enhance treatment efficacy, while potentially reducing the development of drug resistance (Sazawal et al. 2014).

10. Concluding Remarks

Leukemia encompasses complex blood cancers that require a multidimensional approach to

diagnosis and treatment. Genetic polymorphism in various genes (*TPMT*, *UGT1A1*, *ABCB1*, *SLCO1B1*, *BCR-ABL*, and others) is found to be a significant hurdle in achieving optimum treatment response to almost all types of leukemias. Advances in our understanding of leukemia's genetic and molecular underpinnings, and innovations in therapeutic strategies have significantly improved therapeutic outcomes for many patients. However, there is still much work to be done in leukemia research and treatment. Ongoing efforts to refine targeted therapies, harness the power of immunotherapy, and develop personalized treatment plans hold great promise for the future.

Leukemia treatments are becoming more tailored, focusing on minimizing side effects and improving the quality of life for patients. As we look ahead, the goal remains clear: to continue pushing the boundaries of science and medicine to provide the best possible care and outcomes for individuals facing this challenging group of diseases. Healthcare providers, researchers, and patients must continue to collaborate to further these advancements.

Conflict of Interest

The authors declare that they have no competing interests.

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Consent Forms

NA.

Authors Contribution

MN conceptualized the study, SR and MFR helped in the literature review and analysis, MN supervised the whole project and wrote the final manuscript.

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