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Novel Aspects of Leukemia Pharmacogenomics

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Abstract: Acute lymphoblastic leukemia (ALL) is the most common type of leukemia in children between the ages of 2 and 6. It is more frequent in boys than in girls. Currently, the overall cure rate of childhood ALL is approximately 75–80%. Integrated genomic analyses of patients with ALL have advanced the knowledge of the biological basis of ALL and have contributed to identifying subtypes, dysregulated pathways, and therapeutic targets that have resulted in the assignment of stratification categories and improvement of treatment strategies. Genomic studies in pediatric ALL patients have demonstrated chromosomal alterations during the evolution of the disease that directly influence the response to treatment and prognosis. Hence, the proper stratification of patients for identifying risks to prescribe the best treatment is crucial in the management of patients with ALL. Current risk stratification and treatment algorithms include cytogenetic alterations, clinical parameters, and levels of minimal residual disease. All these

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features are integrated to establish the clinical management of patients with ALL for surveillance of treatment success or for the identification of alternative therapeutic approaches. This chapter focuses on the genetic variations that affect the response to most of the chemotherapy drugs used for ALL.

Keywords: genetic variants in acute lymphoblastic leukemia; leukemia pharmacogenomics; pharmacogenetic testing in childhood acute lymphoblastic leukemia; protective pharmacogenetic variants in acute lymphoblastic leukemia; stratification and treatment of patients with acute lymphoblastic leukemia

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a group of neoplasms derived from B- and T-lineage lymphoid precursors and are classified based on their biological and molecular characteristics. The typical B-lineage ALL is observed in most cases (85%), whereas T-lineage ALL is associated with a lymphomatous mass in the mediastinum or other sites. In the last 27 years, there has been an increase in the incidence, prevalence, and mortality of leukemia worldwide; in 2017, there were 0.52 million incident cases, 2.43 million prevalent cases, and 0.35 million deaths, which are often observed in older patients and unhealthy young people (1, 2). A higher incidence among Latino patients has been observed in Mexico, with 57.6 cases observed per 100,000 individuals in a population (3), whereas the 5-year overall survival (OS) is only 50–65% in contrast to the OS of patients who developed the disease in other regions, with an OS corresponding to > 90% and a cure rate of 85%.

Environmental risk factors for childhood leukemia include ionizing and nonionizing radiation (4), chemicals (such as hydrocarbons and pesticides), and parental tobacco use; cigarettes have also been established as being risk factors for leukemia. Ethnicity is also an epidemiological condition for ALL, as it is a poor prognostic factor in Latino populations (5, 6); in addition, the incidence of this disease has increased over the last decade (7). Although the feasible cause remains unknown, socioeconomic status, environmental risks, genetic mutations, or a combination of these factors may contribute to ALL development.

The treatment efficacy has been successful for most patients, and risk factors such as sex, ethnicity, and number of leucocytes have become diminished (8); therefore, its clinical outcome has exceptionally improved. In developed regions, the OS is 5 years, and it has increased over the same period from 60% to approximately 90% for children younger than 15 years and from 28% to more than 75% for adolescents aged 15 to 19 years. Childhood and adolescent cancer survivors require close monitoring because cancer therapy side effects may persist or develop months or years after treatment. Specific information about the incidence, type, and monitoring of late effects in childhood and adolescent cancer survivors is available elsewhere (9).

According to the World Health Organization protocols established in 2008, the diagnoses of ALL include the study of cell morphology, immunophenotype, and genetics/cytogenetics (10, 11). Identification of the morphological bone

marrow cells to differentiate from acute myeloid leukemia (AML) is the first strategy to diagnose ALL. When considering the cellular heterogeneity of ALL subtypes, flow cytometry immunophenotyping is the optimal method for confirming ALL diagnoses and for monitoring minimal residual disease (MRD).

B-cell ALL and T-cell ALL are characterized by recurrent cytogenetic changes (12); therefore, cytogenetics is of great value for the diagnosis, risk stratification, disease monitoring, and treatment selection of ALL. Recent advancements in conventional cytogenetics techniques, such as fluorescence *in situ* hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridization (aCGH), and next-generation sequencing (NGS), have improved classical cytogenetics technologies (13–15).

Pharmacogenomics is the combination of pharmacology and genomics that studies the influence of a person's genetic makeup on response to pharmacotherapy. This chapter focuses on the molecular and genetic basis of known polymorphisms that affect response to drugs most used to treat ALL.

STRATIFICATION AND TREATMENT OF PATIENTS WITH ALL

In general, ALL treatment is designed based on the risk of failure rate, thus allowing for the identification of some clinical characteristics to stratify patients and potentially influence the prognosis. The clinical features include ages less than 1 year and older than 10 years, a white blood cell count (WBC) greater than 50.000–100,000/ml, and the involvement of sanctuary organs (16). Due to recent advances in treatment regimens, the outcomes of T-ALL have improved. The most useful prognostic factor is the response to early treatment, which is estimated by the clearance of leukemic cells from the blood or bone marrow that depends on drug sensitivity or resistance of leukemic cells; additionally, early response is dependent on the pharmacodynamics of the drugs and the pharmacogenetics of the host. Minimal residual disease (MDR) is defined by the presence of 0.01% or more ALL cells and has become a crucial factor for risk stratification in childhood ALL. In addition, it represents a risk of relapse, particularly when measured during or at the end of remission-induction therapy (17).

Current treatment for ALL includes four phases that occur over 2–3 years: induction, consolidation, intensification, and long-term maintenance (18). Pediatric patients with persistent minimal residual ALL are directed to receive an allogeneic hemopoietic cell transplantation that generates a 5-year OS of 79% for low-risk patients and 8% for high-risk patients (19), whereas the OS is 45% in adults. Therefore, the outcome is discouraging compared to the results observed in children (20). It must be assumed that the population of cells from which the tumor arises (cancer stem cells) expresses quiescence and drug resistance, thus hindering the efforts to eradicate them from a patient (21). The treatment phases are as follows:

- *Induction chemotherapy*: This treatment seeks to eliminate malignant burden cells and to restore bone marrow function (22–24).
- *Consolidation therapy*: The goal of this treatment is to prevent the onset of therapy-resistant clones (23).

- *Intensification therapy.* The aim of this treatment is to improve the outcome of patients with a slow early response to therapy (25, 26).
- *Maintenance therapy*: This treatment represents the longer phase and lasts from 2 to 3 years (27).

During this time, clinical features (such as myelosuppression) must be avoided, as it is a predictor of risk relapse (28).

A central nervous system (CNS) prophylaxis should simultaneously be considered with systemic chemotherapy; however, it has been associated with late neurocognitive deficits, endocrinopathy, secondary cancers, and excess late mortality. Therefore, cranial irradiation should be directed to patients with CNS involvement at the time of diagnosis; new therapeutic approaches can include serial intensive intrathecal chemotherapy with methotrexate (MTX) alone or MTX, cytarabine, and hydrocortisone in conjunction with high-dose intravenous MTX and cytarabine (29).

Although hematopoietic stem cell transplantation (HSCT) remains a viable option for those patients with high risk or relapsed ALL, the data on HSCT in patients with disease survival (DS) are limited, and the role in relapsed patients with DS remains unclear (30, 31).

Toxicity

The success of modern treatment approaches for childhood ALL that yield 5-year OS rates above 90% is the result of intense chemotherapy and the respective early response to directed chemotherapy according to treatment stratification by somatic mutations and the optimized use of traditional antileukemic agents, as well as the inclusion of broad-spectrum antibiotics to eliminate opportunistic infections (32). However, a high mortality index of leukemia patients has been observed due to the toxicity of the therapy (rather than by the leukemia itself). To standardize the wide-ranging diversities in toxicity manifestations, the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v6.0 is available for review at the following site: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

CTCAE has defined and graded the toxicities observed during childhood ALL therapy; according to 15 international childhood ALL study groups (Ponte di Legno Toxicity Working Group, or PTWG), the CTCAE has developed consensus definitions for acute toxicities (33). These definitions include mucositis (34), central neurotoxicity (35), peripheral neuropathy (36), bone toxicities (osteonecrosis) (37), thromboembolism (38), sinusoidal obstruction syndrome (veno-occlusive disease) (39), endocrinopathies (especially corticosteroid-induced adrenal insufficiency and hyperglycemia) (40), high-dose MTX-related nephrotoxicity (41) (42), asparaginase-associated hypersensitivity (43), asparaginase-associated pancreatitis (44), and hyperlipidemia (45). Fortunately, most chemotherapeutic drugs have been subjected to pharmacogenetic studies that are useful for adjusting the doses from the beginning of the treatment in individual patients to improve the outcome and to minimize the risks of acute or late side effects.

PHARMACOGENETICS

The accelerated and simultaneous development of molecular pharmacology, biotechnology, and genomics have contributed to revolutionizing the basic principles of therapy and drug development. Pharmacogenetics (PGx) is the branch of pharmacology that focuses on the study of genetic factors that influence the variability of drug responses among patients. As a discipline, it integrates knowledge of the pharmacokinetics (metabolism or disposition of drugs) and pharmacodynamics (efficacy or toxicity of drugs) of each drug (46). Specifically, it focuses on the study of genetic variations in sequences encoding enzymes, drug metabolizers, drug transporters, and drug targets, as well as the effect of the presence of genetic variants on the difference between drug efficacy and toxicity (47).

Over the past decade, PGx has been widely incorporated into pharmacological research and drug development initiatives. The implementation of personalized medicine has future goals of developing polygenic models that accurately predict pharmacological responses and toxicity in individual patients, as well as the use of these models to prospectively personalize treatment regimens to improve efficacy and safety through a better understanding of the patient's pharmacogenetic characteristics (48).

Currently available tools that support personalized medicine and provide up-to-date information for individualizing therapy include the PharmGKB platform (available at http://www.pharmgkb.org), which is a massive resource that provides specialists with relevant information regarding genetic variations and different drug responses. The second PGx resource is the U.S. Food and Drug Administration (FDA) drug labeling database (https://www.fda.gov/drugs). Another knowledge resource is the Clinical Practice Guidelines (CPG) (https://www.nccih.nih.gov/health/providers/clinicalpractice), which lists a set of guidelines for specific diagnostic cases, along with recommended therapeutic action plans (49). Researchers in this area continue to emphasize that their studies should update the general treatment protocols to strengthen them and to improve their effectiveness in patients who are diagnosed with ALL. The treatments that are used are chemotherapy and bone marrow transplantation, and it has been proposed to adopt a personalized treatment (not a generalized treatment) for improving the appropriate doses, which can be designed according to the particular genetic background of each individual (50).

Genetic variants associated with the risk of developing ALL chemotherapy toxicity

Currently, there are several alternative treatment protocols for ALL and all these protocols share many common points. Their implementation has demonstrated very good results or efficacy but also toxicity, thus making this disease an important target for PGx. The typical course of treatment is composed of three main phases and lasts between 2 and 3 years, according to the risk stratification of the disease. Recently, reviews have been published focusing on the evidence of the different responses to drugs in patients diagnosed with leukemia (51).

However, a major disadvantage of PGx research in leukemia is that in each phase of the treatment protocol, patients receive a combination of different drugs and the corresponding toxicities, which are often overlapping, and include hepatotoxicity and myelosuppression. In addition, drug-gene interactions are sometimes influenced by drug–drug interactions, as in the case of 6-mercaptopurine (6-MP) and MTX. Consequently, this circumstance makes it difficult to determine exactly which drug is causing toxicity or to determine the efficacy of PGx for adjusting the dose and for improving efficacy (52).

L-asparaginase

L-asparaginase is one of the drugs that is widely used in the initial chemotherapeutic treatment of ALL (53). Asparaginase is an enzyme originating from several bacterial sources; however, only asparaginases from *Escherichia coli* and *Erwinia chrysanthemi* are used in medicine (54). The function of this enzyme is to catalyze the hydrolysis of the amino acid asparagine (Asn) into aspartic acid (Asp) and ammonia. Leukemic cells do not synthesize Asp (unlike healthy cells); therefore, they depend on its exogenous supply with this mechanism, thus causing the death of the leukemic cell. Among the most representative genetic variants associated with hypersensitivity or toxicity induced by the treatment of this enzyme are *GRIA1* rs4958351, the *ATF5* T1562C variant, *HLA-DRB1* *07:01, *HLA-DQB1* *02:02, rs9272131 close to the *HLA-DQA1* gene, *NFATC2* rs6021191, and *CNOT3* rs73062673. Furthermore, the *PRSS1* rs4726576 variant has been reported to be associated with the risk of developing pancreatitis. Although the presence of the variants or their role in the development of asparaginase hypersensitivity is not yet clear, this effect has been observed in different populations; therefore, it is important to continue with this type of study to provide a more in-depth understanding (55).

Glucocorticoids

Glucocorticoids are part of the induction phase of the chemotherapeutic treatment of ALL. They exert their activity by reducing cell proliferation and by promoting apoptosis or cell cycle arrest by binding to intracytoplasmic glucocorticoid receptors. However, this drug is associated with toxicity in the presence of several variants, such as the haplotype *ABCB1*rs1128503 rs2032582 rs1045642, IL-10rs1800896, or haplotype *NR3C1* rs6189, rs6190, which affects glucocorticoid sensitivity (56). The rs10989692 variants that are close to the *GRIN3A* gene, as well as the *GSTP1* rs1695 and rs1138272 variants, have shown an association with the presence of side effects. Although there have been several studies with this association, there have been considerable discrepancies between the mentioned findings; thus, there is not enough evidence of the effects, and more data are required to consider these variants within routine pharmacogenomic tests (57–60).

Vincristine

Vincristine has the affinity to bind to tubulin dimers, thereby preventing the formation of microtubules and causing the arrest of mitosis and the death of

leukemic cells in metaphase. The presence of toxicity-associated variants has been described in children with ALL who have developed neurotoxicity. Examples of these variants include the *CYP3A5*3* (rs776746) and *CYP3A5*6* (rs10264272 or rs924607), located within the promoter region of the 72 kDa centrosomal protein CEP72. Heterozygous or homozygous genotypes of *CEP72* have been related to neuropathy in different populations; the latter variant is already described in the PharmGKB platform and is associated with neurotoxicity induced by vincristine (11, 23–26).

Methotrexate

MTX is a folate pathway inhibitor and is currently an important component of ALL treatment. MTX suppresses DNA synthesis by competitively inhibiting the enzyme dihydrofolate reductase (DHFR). Genetic variants located in genes encoding enzymes involved in metabolism or transport can significantly affect the absorption, metabolism, excretion, and activity of the drug (27). This drug has a prolonged use during chemotherapeutic treatment; it is also one of the most studied drugs due to the adverse effects that are presented during its administration. Among the genetic variants associated with toxicity due to the administration of this drug, there are some variants located in genes related to cellular processes or leukemogenesis, such as *CCND1* or *ARID5B*. Another important group of genes with pharmacogenetic significant variants are those encoding enzymes involved in the folate pathway, including *DHFR, ITPA, MTR, TYMS*, and *MTHFR*. This group of proteins is key to the *de novo* synthesis of purines and pyrimidines. One of the most studied genes is *MTHFR*. Two variants (rs1801133 and rs1801131) are able to modify the protein sequence, thus consequently causing a reduction in MTHFR activity and an increase in intracellular MTX concentration. The genes encoding input and output drug transport proteins also play an important pharmacogenetic role, particularly the members of the SLC family (*SLC19A1*, *SLC22A1*, *SLC28A8, SLCA6*, and *SLC29A1*). The most relevant variants of this group are *SLCO1B1* rs11045879, rs4149081, and rs4149056, with the presence of these genes having been reported to affect the elimination of MTX, thus causing gastrointestinal and hematological toxicities. Another family of transporters is the ABC family of ATP-binding cassettes (ABCC1, ABCB1, ABCC2, ABCG2, and ABCC4), which are the main MTX output transporters, and the presence of variants in different genes that encode these transporters has been associated with a lower concentration of the different proteins of this family or a decrease in their enzymatic function; as a result, an increase in intracellular MTX levels is observed (1, 28–32).

Thiopurines

6-Mercaptopurine and 6-thioguanine are purine analogs that are metabolically transformed into thioguanine nucleotides (TGNs) that are capable of incorporating into DNA, thus leading to cell death. The presence of variants in different genes has been associated with adverse effects; in addition, thiopurine S-methyltransferase (*TPMT*) is the most studied gene in terms of its pharmacogenomics. This knowledge is useful for the benefit of patients through the

individualization of therapy. Three common variants of the *TPMT* gene (rs1800462, rs1800460, and rs1142345) account for most cases of inherited *TPMT* deficiency. *TPMT* and thiopurines represent one of the first and best documented gene-drug pairs in pharmacogenomics. In addition, the variants *NUDT15**2* (rs746071566) and *NUDT15**3* (rs116855232) in the pharmacogenetic NUDT15 are associated with 6-MP intolerance and are involved in the elimination of 6-MP. An important fact is that these effects been corroborated in multiple studies; thus, the presence of these variants in its sequence is key for the treatment of ALL. Protein kinase C and casein kinase substrate in protein 2 of neurons (*PACSIN2*) have become the focus of attention in the pharmacogenomics of thiopurine drugs, as the presence of the rs2413739 variant demonstrated the strongest association with TPMT activity, although there have been few studies on the association results that have shown congruence in the results (33–40). However, more research is needed to replicate some of these findings, and more concerted efforts are needed to apply this evidence to clinical settings to reduce toxicity from ALL treatment in the pediatric population.

GST genes

The clearance of drugs, such as glucocorticoids, vincristine, anthracyclines, and cyclophosphamide, occurs through the action of a family of enzymes generically named glutathione S-transferase (GST), which are responsible for the inactivation of xenobiotics. The most common polymorphisms described in ALL that influence the risk of treatment success are deletions of the GSTM1 and GSTT1 genes and the A313G substitution in the GSTP1 gene (*GSTP1*B*) (rs1695) (61).

PROTECTIVE PHARMACOGENETIC VARIANTS

As described in the previous section, research studies have focused on the general detection of new genetic variants associated with the metabolism and effect of drugs. These studies have typically focused on the search for, and characterization of risk variants associated with one or more of the adverse effects of either a particular drug or the set of drugs that are used in some phase of treatment. The main reason for this focus is that when a new drug undergoes preclinical and clinical trials, its safety and efficacy are assessed in terms of benefits over risks; thus, when the drug reaches the market, it is assumed to meet the established safety requirements. However, the existence of both risk and protective variants may have a population distribution that was not representative in the testing phases. For comparisons, control groups are integrated with patients whose adverse effects under the same treatment have been null or of a lower risk level, which is ideally matched by age and sex, as well as by follow-up time. Under these circumstances, some genetic variants have been described that are designated as being protective because they are more frequently observed in control groups than in risk groups and are significantly associated with lower toxicities and plasma drug levels. Some examples of such genetic variants are included below, with reference only to the toxic effects of MTX because of space limitations, while also noting that there are variants associated with protection from other drugs and other pathways.

Methotrexate toxicity protective variants

Among the variants that are protective against the toxicity of MTX, the drug that is commonly used in the treatment of ALL is methylenetetrahydrofolate reductase (MTHFR). Among the most studied and relevant drugs are the MTHFR variants rs1801133 and rs1801131. Although studies are numerous, significant evidence of a protective effect is scarce. Hasse et al. (62) described the association between MTHFR rs1801133 and lower blood methotrexate levels, lower risks of anemia and leukopenia, and a lower rate of cycles with infection from a study in Caucasian children. Additionally, Giletti et al. (63) observed that the MTHFR rs1801133 variant has strong protective effects against hematological toxicity caused by MTX. Furthermore, in a Japanese population of pediatric ALL patients, Fukushima et al. (64) described the protection given by the presence of the C allele of the *MTHFR A1298C* (rs1801131) variant that is expressed in lower liver toxicity in carriers. Furthermore, we must not forget that the phenotype of each individual, in addition to the environmental variables that are not discussed in this chapter, are the result of the combination of genetic variants and their interactions. With this observation in mind, there are numerous examples of studies in which haplotypes, and not individual variants, exert a protective effect. For example, patients carrying the *MTHFR 677C-1298C* haplotype have significantly lower plasma concentrations of MTX, as well as less frequent MTX-related toxicities during therapy (65).

Another important molecule involved in folate metabolism and corresponding MTX metabolism is dihydrofolate reductase, which is encoded by the *DHFR* gene, with the *DHFR-* rs1650694 variant of this gene having a clear protective association against hematological toxicity in adult Uruguayan patients with ALL (63).

Regarding the genes encoding the ABC transporter family, two Mexican groups have described protective associations. Zaruma-Torres et al. (66) found that the *ABCB1* rs1128503 and *ABCC5* rs3792585 variants are associated with a protective effect against methotrexate-mediated myelosuppression in children with ALL. Likewise, Ramírez-Pacheco et al. (67) demonstrated that the *ABCB1* rs1045642 variant is protective against leukopenia in homozygotes for the C allele in Mexican children with ALL. Furthermore, Lopez-López E et al. (68) reported that the presence of the G allele of the *ABCC4* rs9516519 variant is associated with lower plasma MTX concentrations and lower toxicity in Spanish children with ALL.

ACTIONABLE PHARMACOGENETIC VARIANTS IN THE TREATMENT OF LEUKEMIA

From the perspective of pharmacogenomics, actionable variants include all the genetic variants that affect drug responses. Under this broad definition, it is correct to include the aforementioned risks and protective variants under this denomination because they are considered in therapeutic decision-making, mainly in the adjustments of doses at which a drug is prescribed or for the use of alternative drugs. These adjustments follow the indications of clinical guidelines that have been developed by organizations such as the Clinical Pharmacogenetic Implementation Consortium (CPIC) or the FDA, when considering the individual's genetic information.

A relevant example of such guidelines is the guideline containing dosing recommendations for thiopurines that are used in the treatment of leukemias, including mercaptopurine for lymphoid neoplasms and thioguanine for myeloid leukemias (69). Dosing guidelines are based on thiopurine methyltransferase (*TPMT*) and nudix hydrolase 15 (*NUDT15*) gene genotypes. Depending on the diplotypes in their different combinations, individuals are classified into normal, intermediate, intermediate potential, poor, and indeterminate metabolizers, for each of which there are specific recommendations for dose adjustments. As the frequencies of each genetic variant may differ between the populations, the relevance of these factors also differs between the populations; therefore, it is important to consider the ancestry of each patient (70, 71). In addition to the reduced risk of unwanted effects, another benefit of lowering the dose of mercaptopurine in the maintenance phase in patients carrying low-activity TPMT alleles is the reduced risk of secondary malignancies (72).

In the case of genes related to methotrexate sensitivity or toxicity, genome-wide association studies (GWAS) have shown that some *SLCO1B1* variants are useful as a reference for dosage adjustments, with a significant decrease in gastrointestinal toxicity associated with faster methotrexate clearance (73, 74), which is key in patients who are treated with high doses of the drug (75).

The list of pharmacogenomic variants related to the drugs that are used in the therapy of leukemia is limited, as only those variants for which there is strong evidence of interactions with one or more drugs are included. However, information continues to be gathered from studies in different populations, and there are variants that stand out as candidates to be considered for validation as actionable variants that are recognized by the specialized organizations mentioned above. Examples of such variants include the human leukocyte antigen haplotypes *HLA-DRB1* *07:01, *HLA-DRB1**16:02, *HLA-DQA1**02:01, and *HLA-DQB1**02:02, which have been linked to asparaginase hypersensitivity (76, 77).

Another drug that is commonly used in the treatment of leukemia is vincristine, which is associated with a risk of neuropathy. Some variants in the cytochromes p450 *CYP3A4* and *CYP3A5*, as well as the variant *CEP72* rs924607 encoding centrosomal protein 72 (78, 79), have been described that produce changes in its expression and that serve as a reference for modifying drug doses. However, the results from different studies have been contradictory, which mainly concerns the *CYP* isoforms (80–82), and this effect is most likely related to the ancestry and genetic background of the studied populations (83). The relevant genetic variants associated with toxicity of chemotherapy in children with ALL described above are summarized in Table 1.

Although interventions that have been implemented as part of the algorithm defining the treatment strategy for leukemia patients are still rare, their use is an extremely valuable tool in reducing deaths and severe adverse events related to chemotherapy. It is essential to expand studies that are focused on both the discovery of new variants that are likely to be actionable and their validation in populations with different ancestry so that the benefits of pharmacogenomics can be extended on a global scale.

TABLE 1 **Relevant genetic variants associated with toxicity of chemotherapy in children with ALL**

Gene	Variant	Level&	Drug	Gene	Variant	Level	Drug
ABCB1	rs1128503 #	3	Methotrexate	ITPA	rs1127354	4	Mercaptopurine
ABCB1	rs1045642 #	3	Methotrexate	MTHFD1	rs2236225	3	Methotrexate
ABCC2	rs717620	3	Methotrexate	MTHFR	rs1801133 #	4	Mercaptopurine
ABCC4	rs7317112	3	Methotrexate	MTHFR	rs1801131 #	4	Methotrexate
ABCC4	rs9516519#	3	Methotrexate	MTHFR	rs1801131	4	Methotrexate
ABCC5	rs3792585	NA	Methotrexate	MTHFR	rs1801133	2A	Methotrexate
ABCG2	rs2231142	4	Methotrexate	MTR	rs1805087	4	Methotrexate
ARID5B	rs4948496	3	Methotrexate	MTRR	rs1801394	3	Methotrexate
BCL2L11	rs2241843	3	Corticosteroids	NFATC2	rs6021191	3	Asparaginase
BCL2L11	rs724710	3	Corticosteroids	NUDT15	rs746071566	3	Mercaptopurine
BMP7	rs79085477	3	*	NUDT15	rs766023281	3	Mercaptopurine
CAT	rs10836235	3	Anthracyclines and related substances	NUDT15	NUDT15*1; NUDT15*2; NUDT15*3	1A	Mercaptopurine
CCND1	rs9344	3	Methotrexate	PACSIN2	rs2413739	3	Mercaptopurine
CEP72	rs924607 @	3	Vincristine	PACSIN2	rs2413739	3	Mercaptopurine; Methotrexate
CPA2	rs199695765	3	Asparaginase	PNPLA3	rs738409	3	***
DHFR	rs1650694#	NA	Methotrexate	SERPINE1	rs6092	3	Dexamethasone

(Continued)

TABLE 1 **Relevant genetic variants associated with toxicity of chemotherapy in children with ALL (*Continued*)**

Gene	Variant	Level&	Drug	Gene	Variant	Level	Drug
DHFR	rs442767	3	Methotrexate	SHMT1	rs1979277	3	Methotrexate
DHFR	rs70991108	3	Methotrexate	SLCO1B1	rs4149081	3	Methotrexate
DHFR	rs408626	3	Methotrexate	SLCO1B1	rs4149056	3	Mercaptopurine; methotrexate
DOK5	rs117532069	3	*	SLCO1B1	rs11045879	3	Mercaptopurine
DROSHA	rs639174	3	**	SLCO1B1	rs11045879	4	Methotrexate
FOLH1	rs61886492	3	Mercaptopurine; Methotrexate	SOD2	rs4880	3	Asparaginase
GOGH	rs11545078	3	Methotrexate	TPMT	TPMT*1; TPMT*21; TPMT*33; TPMT*34	3	Thioguanine
GNMT	rs10948059	3	Mercaptopurine	TPMT	rs1142345	3	Mercaptopurine
GRIA1	rs4958381	3	Asparaginase	TPMT	TPMT*1; TPMT*21; TPMT*33; TPMT*34	3	Mercaptopurine
GSTP1	rs1695	3	Mercaptopurine; methotrexate	TPMT	TPMT*1; TPMT*21; TPMT*33; TPMT*34	3	Thioguanine
HLA-DRB1	rs17885382[@]	3	Asparaginase	TPMT	TPMT*1; TPMT*21; TPMT*33; TPMT*34	3	Mercaptopurine
ITPA	rs7270101	3	Mercaptopurine; methotrexate	TYMS	rs11280056	3	Methotrexate
ITPA	rs1127354	3	Methotrexate	TYMS	rs45445694	3	Methotrexate

[#]Also described as protective variant or [@]actionable variant. [&]Level of evidence to PharmaGKB: Level 1, variant with proven association; level 2, moderate levelof support; 3, low level of evidence supporting the association; and 4, very little information and discrepancies between results. NA not annotated. *Cyclophosphamide; cytarabine; daunorubicin; dexamethasone; doxorubicin; methotrexate; pegaspargase; prednisone; thioguanine; vincristine. **Cyclophosphamide; cytarabine; daunorubicin; mercaptopurine.

PHARMACOGENETIC TESTING IN CHILDHOOD ALL

There is currently sufficient evidence demonstrating the need for the implementation of personalized medicine. Regarding childhood ALL, there are two established pharmacogenetic tests that detect variants in the TPMT and NUD15 genes (due to the fact that the presence of variants in these genes interferes with the metabolism of drugs such as thioguanine and 6 mercaptopurine, which impacts their enzymatic function), thus requiring dose adjustments in patients who present these genotypes. The most commonly available clinical PGx tests that are used worldwide are those that detect variants of these genes, but many institutions still do not offer these tests, especially in developing countries. The tests are accredited by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the FDA, and the European Medicines Agency (EMA) (41, 42).

There are significant challenges associated with drug implementation, such as laboratory or hospital infrastructure factors, costs, profit, and lack of knowledge or skepticism of physicians. However, we can conclude that the efficacy of different anti-leukemia drugs is affected by genetic variants; therefore, it may be much more cost-effective and practical to perform a preventive PGx test to avoid adverse effects, thus improving the patient's quality of life and allowing for the implementation of an individualized therapy that improves survival prognoses (43).

CONCLUSION

ALL is the most common pediatric cancer and is characterized by the expression of lymphoid cell surface markers. The treatment effectiveness has improved for most patients, as risk factors such as sex, ethnicity, and the number of leucocytes has become diminished. The specific molecular alterations and modifications in critical pathways of leukemogenesis have been achieved with the use of modern tools that have increased our knowledge related to lymphoblastic leukemias, which has allowed for the improvement of the survival of patients suffering from this disease. In addition, current functional studies of basic genetic alterations identified in ALL patients have contributed to a better understanding of ALL pathogenesis and the management of this disease. The application of individualized strategies, especially in children, based on the integration of knowledge related to the biology of tumor cells, the pharmacodynamics of the drugs, and particularly the pharmacogenetics that values the impact of multiple mutations in the genome of the host to determine the patient's response to drug therapy, could guarantee a better outcome for each patient.

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