Translational Oncology 14 (2021) 100978

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Promising genes and variants to reduce chemotherapy adverse effects in acute lymphoblastic leukemia

Diego Alberto Bárcenas-López[a,b], Diana Karen Mendiola-Soto[a,c], Juan Carlos Núñez-Enríquez[d], Juan Manuel Mejía-Aranguré[d,e], Alfredo Hidalgo-Miranda[a], Silvia Jiménez-Morales[a,*]

[a] Laboratorio de Genómica del Cáncer, Instituto Nacional de Medicina Genómica, Periferico Sur 4809, Arenal Tepepan, Del. Tlalpan, Mexico City 14610, Mexico
[b] Programa de Doctorado, Posgrado en Ciencias Biológicas, Universidad Nacional Autónoma de México, Mexico City, Mexico
[c] Programa de Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México, Mexico City, Mexico
[d] Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Pediatría, CMNSXXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico
[e] Coordinación de Investigación en Salud, Instituto Mexicano del Seguro Social, Mexico City, Mexico

ARTICLE INFO

Keywords:
Acute lymphoblastic leukemia
Pharmacogenes
Polymorphisms
Treatment response
Personalized medicine

ABSTRACT

Almost two decades ago, the sequencing of the human genome and high throughput technologies came to revolutionize the clinical and therapeutic approaches of patients with complex human diseases. In acute lymphoblastic leukemia (ALL), the most frequent childhood malignancy, these technologies have enabled to characterize the genomic landscape of the disease and have significantly improved the survival rates of ALL patients. Despite this, adverse reactions from treatment such as toxicity, drug resistance and secondary tumors formation are still serious consequences of chemotherapy, and the main obstacles to reduce ALL-related mortality. It is well known that germline variants and somatic mutations in genes involved in drug metabolism impact the efficacy of drugs used in oncohematological diseases therapy. So far, a broader spectrum of clinically actionable alterations that seems to be crucial for the progression and treatment response have been identified. Although these results are promising, it is necessary to put this knowledge into the clinics to help physician make medical decisions and generate an impact in patients' health. This review summarizes the gene variants and clinically actionable mutations that modify the efficacy of antileukemic drugs. Therefore, knowing their genetic status before treatment is critical to reduce severe adverse effects, toxicities and life-threatening consequences in ALL patients.

Introduction

Acute lymphoblastic leukemia (ALL) is the commonest childhood cancer worldwide, accounting for approximately 80% of all childhood leukemias [1,2] and more than 349,000 newly cases were diagnosed in 2018 over the world [3]. ALL is a serious problem for developing countries, especially in Latin America, where the incidence of lymphoid leukemias is among the highest in the world and overall survival (OS) rates are lower compared to high-income countries (HIC) [4–7]. Currently, with risk-adapted stratification of patients, the development of targeted therapies in combination with conventional chemotherapy and the identification of novel molecular subtypes, OS in childhood ALL from HIC exceeds 90% at 5-years of follow-up but it is significantly lower in developing countries [5,8]. Furthermore, some patients relapse during early phases of therapy or develop resistance to treatment (either intrinsically or acquired resistance), and even those cases who are considered cured could suffer lifelong sequelae due to chemotherapy [9,10]. These survival rates disparities between racial groups are also evident in developed countries, as it has been observed in Hispanics in the United States, where high-risk clinical features and lower outcomes are common [11,12]. It is well known that social and demographical aspects like low quality of care due to deficiencies in health infrastructure have a direct impact in mortality rates. Nonetheless, biological factors such as genetic variants and epigenetic processes are also determinant in the disease progression and in treatment response [7]. In fact, these aspects can also explain inter-individual and inter-population variations in the antileukemic drugs metabolism [11]. Identifying genes involved in drug response variability, also known as pharmacogenes, and detecting their genetic variation that influence both pharmacological efficacy and treatment toxicity, represents a big challenge [13].

The development of high throughput technologies in the last decade such as microarrays and next generation sequencing have allowed us to increase our knowledge about the genetic alterations that modulate drugs efficacy for many human diseases, particularly in cancer [14,15]. Due to their biological impact in the protein activity, studies of common germline variants as single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) in pharmacogenes, in addition to somatic

* Corresponding author.
E-mail address: sjimenez@inmegen.gob.mx (S. Jiménez-Morales).

https://doi.org/10.1016/j.tranon.2020.100978
Received 6 October 2020; Received in revised form 17 November 2020; Accepted 25 November 2020
1936-5233/© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

mutations (mainly point mutations, gene deletions and gene fusions) have been the major targets of pharmacogenomics studies. Thiopurine S-methyltransferase (*TPMT*), nudix hydrolase 15 (*NUDT15*), solute carrier organic anion transporter family member 1B1 (*SLCO1B1*), ATP Binding Cassette Subfamily B Member 1 (*ABCB1*), retinoid acid receptor gamma (*RARG*), solute carrier family 28 member 3 (*SLC28A3*), and UDP glucuronosyltransferase family 1 member A6 (*UGT1A6*4*) are some examples of the potential useful pharmacogenes. Incorporating other relevant genes like 5′-Nucleotidase, Cytosolic II (*NT5C2*), phosphoribosyl pyrophosphate Synthetase 1 (*PRPS1*) and Nuclear Receptor Subfamily 3 Group C Member 1 (*NR3C1*) into the ALL treatment is still a pending task, as these genes are frequently mutated in relapsed ALL and there is evidence that highlights their usefulness into clinical applications. This review summarizes the current understanding and emerging insights of genes and treatment in ALL.

Diagnosis, risk classification and treatment

ALL is a fast-growing malignancy originated from lymphoid progenitor cells in the bone marrow and comprises a highly clinical and genetically heterogeneous disease. Presenting symptoms are non-specific; however, fever, brushing, skin pallor, petechia, bone pain, weakness, night sweats, and weight loss are common in ALL pediatric patients. More than a half of the cases have hepatosplenomegaly, mental changes and oligouria; testicular enlargement and mediastinal mass could be also present [16]. Diagnosis of ALL is established by morphological and immunophenotypical features of the bone marrow cells aspirate. A leukemic blasts percentage >25% confirms ALL disease, while flow cytometry identifies precursor B-cell, T-cell, and mature B-cell immunophenotypes, in 80%, 15%, and 5% of the pediatric patients, respectively [17].

Since decades ago, diverse protocols have been designed to treat leukemia, but the treatment based on the patients' risk for relapse gives the best OS rates. Based on clinical features (age and leukocyte count), immunophenotypical and genetic characteristics of the leukemic cells, current treatment regimens stratify childhood ALL patients in risk groups (as example, St Jude protocol identifies low/standard risk, high risk and very high risk groups) to reduce toxicity. The standard treatment based on chemotherapy is indicated for the low risk-group. Meanwhile, in addition to chemotherapy, protocols that include radiation therapy, hematopoietic stem cell transplant (HSCT), targeted therapy (like tyrosine kinase inhibitors or TKIs) and chimeric antigen receptor (CAR) T-cell therapy are suitable for high risk and very high risk groups [5,18]. All protocols comprise three phases: a) remission induction (0–28 days) to restore normal hematopoiesis, b) consolidation (29–60 days) and c) maintenance (2 < 36 months), whose purpose is to eradicate residual leukemic cells. Patients who do not reach remission during the first month or relapse after the completion of primary treatment, undergo a second remission induction phase. In all cases, drugs such as vincristine, asparaginase, daunorubicin, glucocorticoids, cyclophosphamide, cytarabine and methotrexate are administered during the first two phases of therapy, and nucleoside analog drugs as thiopurines (mercaptopurine and thioguanine) are central agents in the maintenance phase (Fig. 1) [10,19].

Germline variants, mutations and treatment response

The current OS among ALL cases has dramatically improved with the increasing knowledge of the genetic background of ALL patients and its association with the treatment response. Novel information about the genomic features of leukemic cells allowed us to identify specific molecular targets. It is well known that variants and mutations in genes influencing the drug absorption, distribution, metabolism and excretion explain the differences in drug response between patients. In this regard, *BCR-ABL, TPMT, NUDT15*, among others, have been recognized as relevant contributors to improve clinical management of ALL cases (Fig. 2).

TPMT

Thiopurines as 6-thioguanine (6-TG), 6-mercaptopurine (6-MP) and azathioprine are commonly used in the treatment of many types of cancer, autoimmune diseases, and critical in the maintenance phase for ALL patients. Thiopurines are prodrugs metabolized into thioguanine nucleotides (TGN), which are purine analogs used to arrest the cell cycle and to induce apoptosis by TG incorporation into the DNA [20]. One of the key genes involved in thiopurine metabolism is *TPMT,* which encodes for the enzyme that catalyzes the S-methylation of thiopurine drugs. Over 37 SNPs have been associated with decreased enzyme activity compared to the wild-type gene (*TPMT*1*) and variable number of tandem repeats (VNTRs) in the promoter region have been found as correlated with *TPMT* low expression [20,21]. The rs1800462 (p.Ala80Pro), rs1800460 (p.Ala154Thr) and rs1142345 (p.Tyr240Cys) SNPs are the most common variants worldwide and the mutant alleles *TPMT**2 (rs1800462), *TPMT**3A (rs1800460 and rs1142345), *TPMT**3B (rs1800460) and *TPMT**3C (rs1142345) have significant evidence on their clinical utility [22,23]. Patients who are homozygous or compound heterozygous for mutant *TPMT* alleles display a nonfunctional TPMT enzyme, which leads to high levels of TGN and risk to develop severe myelotoxicity during treatment with standard doses of thiopurines. Meanwhile, patients with only one non-functional allele could likely experience toxicity, thus, the Food and Drug Administration (FDA) strongly recommends a reduction from 30 −70% and up to 10-fold reduction of daily doses in patients with two nonfunctional alleles [24]. Besides the mutant alleles of *TPMT*, it has been reported that homozygous of VNTR*5a/*5a show high expression levels of the enzyme, while those carrying VNTR*7th allele had lower *TPMT* expression [20]. This could have an impact by compensating *TPMT* in patients who are intermediate metabolizers by modulating gene expression levels based on VNTR architecture. *TPMT* genotypes have also been associated with event-free survival (EFS), as carriers of one *TPMT* mutant allele (heterozygous) have better EFS than the *TPMT*1* patients. It is possibly that high intracellular accumulation of TGNs in heterozygous patients could influence the high efficacy of the treatment of these cases [25]. Otherwise, evidences suggest that low or absent TPMT activity increase the risk to develop secondary tumors but reduce the risk to relapse [26].

Despite the importance of *TPMT* genotyping and knowing that certain risk alleles are well established as markers of potential thiopurine toxicity, patients homozygous for the WT allele might have adverse effects too. The importance of other genes involved in thiopurine metabolism like *NUDT15* has been addressed, which also has a determinant role in the metabolism of thiopurine drugs.

NUDT15

NUDT15 gene encodes for a member of the nudix hydrolase enzyme family that converts thioguanine triphosphate (TGTP) to thioguanine monophosphate (TGMP) by negatively regulating the activation of thiopurines. Genetic variants in *NUDT15* like rs116855232 (p.Arg139Cys), rs147390019 (p.Arg139His), rs186364861 (p.Val18Ile), rs869320766 (p.Val18_Val19insGlyVal), p.Lys35Glu (no rsID), rs746071566 (p.G17_V18del) and the recently described rs766023281 (p.Arg34Thr) have been associated with a deficient activity of the enzyme, which causes poor metabolism of thiopurines, elevated levels of toxic metabolites and myelosuppression. These variants either affect the protein stability or their interactions with its substrate, resulting in a reduction from 75 to 100% of NUDT15 enzymatic activity [27,28]. As example, Moriyama et al., observed that p.G17_V18del variant derives in a protein with low thermostability displaying total loss of its catalytic activity [29]. The p.Arg139Cys also seems to relate with the stability of the protein, particularly in an α-helix at the thiopurine binding pocket

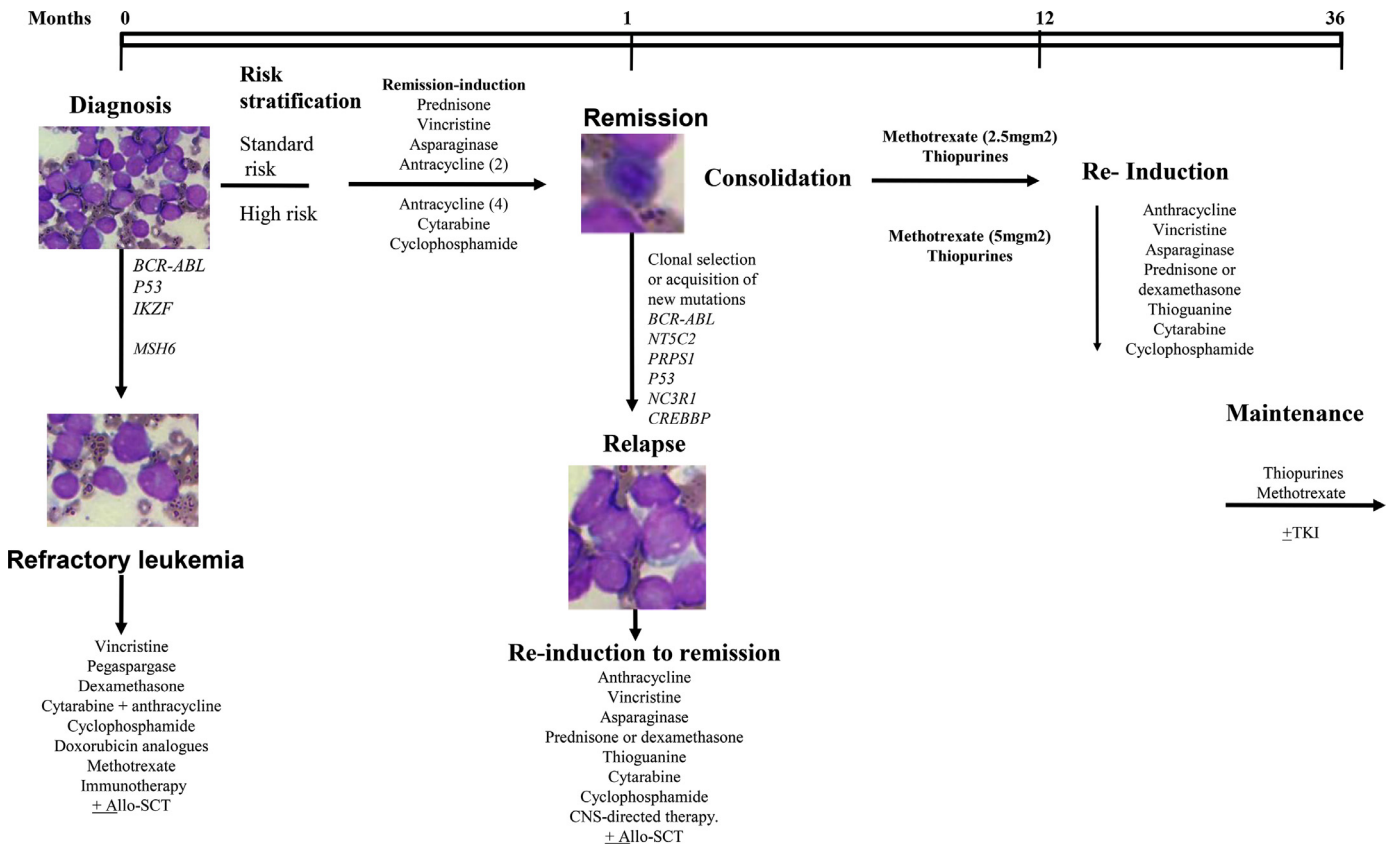

Fig. 1. Chemotherapeutic treatment schedule for pediatric acute lymphoblastic leukemia. Different chemotherapeutic agents in different doses are administered depending on patient's classification risk in each of the treatment's phases: remission induction (0–28 days), consolidation (29–60 days) and maintenance (>2 - 36-months). The selection of these agents is also defined by patient's response and acute lymphoblastic leukemia evolution in which mutation of specific genes are known to be involved.

site [30]. *NUDT15* polymorphisms also show differential distribution among populations [28,31,32]. For instance, the p.Arg139Cys variant (T risk allele), significantly associated with 6-MP-induced leukopenia, has been found in 9.8% in East Asians, 3.9% Hispanic populations, but very rarely in Europeans and non-existent in African populations [32]. Meanwhile, the p.Arg34Thr, p.Lys35Glu, and p.G17_V18del have been detected only in European and African patients [29]. Although their effect along with SNP in other genes involved in thioguanine metabolic pathways remains poorly studied, it is suggested that *NUDT15* genotyping is useful to standardize the tolerated dose of 6-MP in children with ALL [33]. It is recommended a reduction of 50% of the normal dose in those cases with at least one *NUDT15* deficient allele [31–34].

RARG

Retinoic acid receptors (RAR) bind to DNA regulatory sequences termed retinoic acid response elements (RARE) and transcriptionally co-regulate downstream gene expression in response to their agonist all-trans retinoic acid (ATRA) [35]. RARgamma (RARG), also known as *NR1B3,* encodes a nuclear receptor that can both activate and repress transcription in response to ATRA [36]. This gene belongs to the nuclear receptor superfamily and shares 90% homology with the other two members, *RARA* and *RARB* [35]. RARG plays a central role in maintaining the balance between the self-renewal state of hematopoietic stem cells (HSCs) and their differentiation [37]. Anthracyclines are used in most of ALL treatment protocols and cumulative dose has been described as one of the causes of cardiac dysfunction and congestive heart failure in pediatric patients [38,39]. Aminkeng et al., reported that the nonsynonymous variant rs2229774 (p.Ser427Leu) in *RARG* was significantly associated with anthracycline-induced cardiotoxicity (ACT) in childhood cancer patients [40]. Although rs2229774 in *RARG* was more frequent in cases with European ancestry, this association was also replicated in non-Europeans [40]. This variant alters RARG function leading to derepression of the key ACT genetic determinant Topoisomerase II beta (*Top2b*) [40]. Anthracyclines exert their anticancer activity by binding and inhibiting Topoisomerase II [41]. The Ser427Leu allele does not repress *Top2b* expression as effectively as wild type *RARG. In vitro* studies showed that even though rs2229774 causes a well-tolerated amino acid substitution, still results in a significant reduction in transcriptional activation from RARE elements [40,42].

SLC28A3

The SLC28 family has three members of sodium-dependent, concentrative nucleoside transporters: concentrative nucleoside transporter (CNT) 1, CNT2, and CNT3 (SLC28A1, SLC28A2, and SLC28A3, respectively). These proteins are responsible for high-affinity transport of both naturally occurring nucleosides and synthetic nucleoside analogs used in the treatment of cancer and viral drugs. SLC28A3 transports both pyrimidine and purine nucleosides into cells in a sodium-dependent manner. High levels of *SLC28A3* mRNA transcripts are found in the pancreas, trachea, bone marrow, and mammary gland [43]. Moreover, it has been observed that SLC28A3 can transport several anthracyclines drugs including doxorubicin into cells, providing a potential mechanism by which these variants could affect ACT. Studies have provided evidence for the association among of rs7853758 (p.Leu461Leu) and rs885004 (Leu248Leu) with ACT [40,44]. The most consistent results were found between the minor allele rs7853758 461Leu with ACT [44–46], which is also associated and with reduced *SLC28A3* mRNA expression in monocytes [47]. Although scarce evidences regarding the role of this SNP in

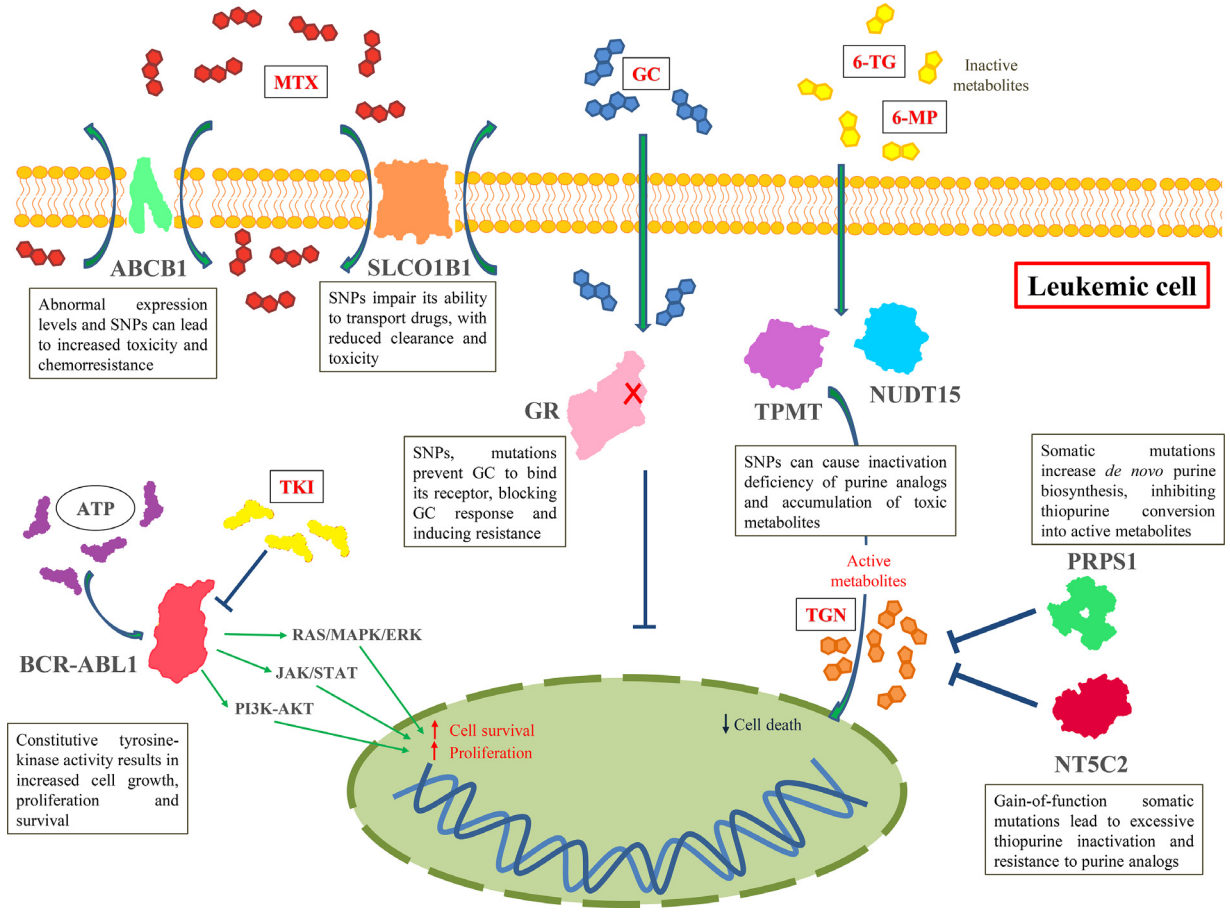

Fig. 2. Genes of therapeutic relevance in acute lymphoblastic leukemia. The figure depicts the most common functional polymorphisms, somatic mutations and fusion oncoproteins involved in chemotherapy response, metabolism, transport and clearance of the most widely used drugs in ALL treatment. MTX: methotrexate; GC: glucocorticoids; 6-TG: 6-thioguanine; 6-MP: 6-mercaptopurine; ATP: adenosine triphosphate; TKI: tyrosine kinase inhibitor; GR: glucocorticoid receptor; TGN: thioguanine nucleotides; SNP: single nucleotide polymorphism.

ALL, there is a recommendation for genetic testing to all patients under anthracyclines treatment to reduce the incidence of ACT [40,46].

*UGT1A6*4*

Glucuronidation is an important pathway in the detoxification and elimination of many drugs and is catalyzed by the UDP-glucuronosyltransferases (UGTs) superfamily of enzymes [48]. UGT1A6 is a phenol-specific enzyme that catalyzes glucuronidation and subsequent elimination of a diverse range of drugs, toxic xenobiotics and endogenous substrates [49]. The UGT1A family is encoded by a single nested gene *locus* spanning 200 kb on chromosome 2q37 [50]. The synonymous variant p.Val209Val (rs17863783) has been associated with an increased risk of ACT in pediatric patient with ALL from several populations [45,46]. As well, rs17863783 is a tag marker of the *UGT1A6 *4* haplotype, which has been reported to cause a 30–100% reduction in enzyme activity [49,51]. Since *UGT1A6* plays a determinant role in glucuronidation-mediated drug detoxification, patients carrying *UGT1A6 *4* haplotype could have an increased ACT risk due to accumulation of toxic metabolites when treated with anthracyclines [42]. Recently, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Practice Recommendations Group found that *UGT1A6*4* rs17863783, *RARG* rs2229774 and *SLC28A3* rs7853758 variants have strong evidence to define them as pharmacogenomic markers for ACT. Therefore, their pharmacogenomic testing is strongly recommended in all childhood cancer patients with an indication for doxorubicin or daunorubicin therapy [52].

SLCO1B1

Membrane transporters are essential in the influx and efflux of wide variety of compounds, nutrients, small molecules and ions. In cancer treatment, they play a key role in maintenance of chemotherapy drugs inside the cell or exporting them out of the cell. Among the family of transporters, solute carrier (SLC) family transporters have gained interest not only as regulators of drug transport, but as nutrient uptake mediators that promote growth and survival of cancer cells. The *SLCO1B1* gene is the most explored in leukemia. *SLCO1B1* encodes for a liver-specific transmembrane sodium-independent transporter protein involved in the active influx of many endogenous compounds like bilirubin, hormones and drugs for their removal from the body [53,54]. Evidences suggest that polymorphisms in *SLCO1B1* may impair its transporter activity for chemotherapy agents, including metothrexate (MTX) [55]. It has been reported that genetic variants in this gene substantially influence MTX transport and toxicity risk in childhood ALL [56]. Of these variants, the rs4149056 (p.Val174Ala) has been associated with *SLCO1B1* loss-of-function and with reduced MTX clearance [57,58]. The rs4149056 (Val174Ala) has been significantly associated with lower event-free survival rates and persistence of minimal residual disease (MRD), and the rs10841753 with lower plasma MTX levels in pediatric ALL patients [59]. Due to most of chemotherapy protocols for childhood ALL includes MTX and it is well known that this drug may cause potentially severe adverse effects and toxicities that can be life-threatening, it is suggested the *SLCO1B1* genotyping before treatments based on MTX [59,60].

NR3C1

Glucocorticoids (GC), such as prednisone, prednisolone and dexamethasone are considered the backbone of chemotherapy regimen, and they were some of the first drugs used in ALL treatment. Given their immunosuppresor effects, they are also used to treat autoimmune-mediated diseases such as asthma, rheumatoid arthritis and lupus, showing their relevance in the pharmacogenomics field [61]. The knowledge about GC as cytotoxic agents derives mainly from the treatment of childhood leukemia [62]. These drugs exert their cytotoxic function by binding to the glucocorticoid receptor (GCR), a nuclear receptor ligand-activated transcription factor encoded by the *NR3C1* gene. GCR dimerizes and translocates to the nucleus, leading to the expression of genes involved in cell survival, proliferation and glucose metabolism, among others biological processes [63,64]. Patients that display GC resistance during the treatment have an increased risk of relapse, making GC response as one of the most useful prognostic factors in ALL [65]. The mechanism underlying lymphocytes GC cell death induction is not well understood; however, evidences show that SNPs and somatic mutations in *NR3C1* could contribute to GC resistance in ALL patients. GCR polymorphisms rs56149945 (p.Asn363Ser*)* and rs41423247 have been associated with corticosteroid response and high sensitivity to methylprednisolone in human lymphocytes *in vitro* and prednisone response [66–68], but also with side effects derived (as hepatotoxicity) from GC-based treatment and disease outcome in childhood ALL [68–71]. Somatic *NR3C1* gene deletions have been detected at diagnosis and conserved at relapse in some cases. In fact, 10% of *ETV6-RUNX1*+ children with poor response to induction treatment have deletions in *NR3C1* [72]. Additionally, *NR3C1* is found frequently mutated in relapsed ALL and all mutations identified so far are truncated mutations (*e.g.*, p.D144Efs x11) inducing haploinsufficiency of the NR3C1 protein [73]. Experimental evidences showed that GCR defects could be decisive for glucocorticoid resistance, and that ectopic expression of GCR abates GC resistance in ALL cell lines and xenograft models with *NR3C1* haploinsufficiency [74,75]. It has been suggested that the Bcl-2 blocking to induce GC response in *NR3C1* mutated ALL cells, as Bcl-2 is the major negative regulator of *NR3C1* [75].

ABCB1

ATP Binding Cassette Subfamily B Member 1 (*ABCB1*) encodes for the transporter protein MDR1 (multidrug resistance 1), also called P-glycoprotein (P-gp). It is responsible of xenobiotics transport, acting as an ATP-dependent drug efflux pump and therefore contributing to chemorresistance by the active transport of drugs outside of the cell, decreasing the intracellular levels of chemotherapy agents. Among the 50 SNPs identified in this gene; the rs1045642 (C3435T), a synonymous variant at codon 1142 (Ile1142Ile) is the most widely studied [76–78]. Minor allele 3435T has been associated with decreased mRNA expression, altered substrate specificity and low protein stability [79–81], ultimately causing a reduced transporting activity [82]. Although there is differential distribution among populations, studies in ALL patients have reported that carriers of the 3435TT allele have higher risk of ALL development, bone marrow toxicity and lower EFS after doxorubicin, vincristine and prednisolone administration in comparison with homozygotes to the wild type allele [77]. Otherwise, patients with homozygote CC genotypes have higher risk to liver toxicity after high doses of MTX treatment [77,83–85]. Other variants like the rs128503 (C1236T) and rs2229109A (1199G>*A*) have been associated with high risk to develop ALL and relapsed ALL, respectively [77,85]. Low survival of ALL patients has been also observed in cases with high *ABCB1* gene expression; however, it has been reported that these patients have better outcome after using metformin alongside chemotherapy [86].

BCR-ABL1-Positive and Ph-like phenotype

The treatment of *BCR-ABL1*-Positive and Ph-like is one of the most successful examples of genetic and genomic characterization of novel subtypes and their molecular features in ALL. The use of tyrosine kinase inhibitors (TKIs) as first-generation TKI like imatinib, second- and third-generation TKIs (dasatinib, nilotinib, bosutinib and ponatinib) and other kinase inhibitors (ruxolitinib for JAK-driven alterations) in combination with cytotoxic chemotherapy have substantially increased OS and reduced the need of HSCT during the first remission in *BCR-ABL1* (Ph+ ALL) patients [87,88]. TKIs are also beneficial to the Ph-like subtype, a recently described molecular subtype of B-ALL that exhibits a gene expression profile similar to *BCR-ABL1*+ patients but lacks this recurrent fusion gene. Concomitant loss-of-function mutations in *IKZF1* and *CDKN2A/B* are frequent in Ph-like cases, but mutations that activate cytokine receptors (*CRLF2, PDGFRB, CSF1R*) and kinase signaling pathways (Janus kinases, *ABL1, ABL2*) are the hallmark of this subtype, which is also associated with poor prognosis and Hispanic ethnicity [89]. Ph-like phenotype shows different frequencies among age and risk groups, being less common in children (standard risk: 10% and high risk: 15%) than adolescents (21%), young adults (>27%), and older adults (>40 years old: 10–20%) [89–91]. Although Ph-like is a clinically aggressive subtype (hyperleukocytosis at diagnosis and persistent MRD), these patients also benefit with TKIs treatment [90,92]. Resistance to TKIs during the first-line or subsequent-line therapies has been documented, albeit the patterns of kinase domain (KD) mutations in Ph-positive pediatric ALL are still unknown. *BCR-ABL* adults with chronic leukemia and ALL have acquired point mutations (T315I, G250E, Q252H, Y253H/F, E255K/V) that induce TKI resistance [93,94]. KD mutations are also associated with shorter OS; therefore, the identification of *BCR-ABL1* subclones could improve the therapeutic management based on TKIs in *BCR-ABL1*+ patients.

Pharmacogenes associated with ALL relapse

Although major improvements in ALL treatment have been achieved, relapsed ALL occurs in around 15–20% of childhood patients around the world. In fact, if considered as a separate entity, relapsed ALL represents the fourth most common childhood cancer and one of the leading causes of cancer-related deaths in children [95]. Leukemic blasts at relapse are usually more resistant to chemotherapy than blasts at diagnosis, and clones could be either selected by the treatment (present as minor subpopulations at diagnosis) or arise from different subclones with chemotherapy-acquired mutations [96]. Relapse-specific mutations have been described in over 12 genes, 46% of them in *NT5C2, PRPS1, NR3C1*, and *TP53* [97,98]. Notably, *NT5C2* and *PRPS1* are involved in thiopurines metabolism and *NR3C1* in glucocorticoids drug response (described above), showing that relapse could be induced by additional mutations acquired during chemotherapy treatment [98]. Relapsed ALL prognosis is dismal and developing strategies to treat these patients is of utmost importance. In this regard, *NT5C2* and *PRPS1* rise as promising therapeutic targets [97,100].

NT5C2

NT5C2 gene encodes a 5′-nucleotidase enzyme that catalyzes the 5′ -dephosphorylation of purine nucleotides and is involved in the intracellular nucleoside pool homeostasis by facilitating the exportation of purine nucleosides out of the cell [101]. NT5C2 also metabolizes nucleoside-analog drugs including 6-MP and 6-TG, which constitute the backbone of maintenance phase of chemotherapy. NT5C2 mutant proteins show increased nucleotidase activity *in vitro,* inducing depletion of the purine-nucleotide pool inside the cell and resistance to nucleoside analogs drugs [102,103]. Over 32 mutations in *NT5C2* have been described and at least 25 different mutation specifically in relapsed ALL [104]. Gain-of-function mutations are common events at

relapse in both B-ALL and T-ALL, especially in early relapses (from 3 to 45% and 19to 38% for relapsed B-ALL and T-ALL cases, respectively) [97,98,102,103,105,106]. Although a wide array of *NT5C2* mutations is known, their mechanisms of activation differ between them. Three classes of mutations are proposed, the most frequent being mutations that disrupt the switch-off mechanism of NT5C2 [107]. Structural and biochemical studies showed that leukemic cells carrying the most common mutation, p.R367Q (c.1100G>*A*) display excessive exportation of purines and causes loss-of-fitness phenotype, cell growth impairment and leukemia-initiating cell activity [106–109]. Other mutations like p.K359Q act in a constitutively active state, leading to excessive nucleotidase activity and poor prognosis [107,109]. As well, it has been reported that 90% of mutations described in leukemia are located into 3 hot spots (residues 232–242, 355–365, and 400–418) and *in silico* analysis suggests that these mutations drive chemoresistance and relapsed in leukemia [104]. Evidence proposes that *NT5C2* mutations driving chemotherapy resistance arise during the late events of the clonal evolution of relapsed ALL, pointing out the NT5C2 inhibitors as promising targets to switch the thiopurine resistance due to gain-of-function *NT5C2* mutations [107,109,110].

PRPS1

The ribose-phosphate diphosphokinase 1 encoded by *PRPS1* gene is a rate-limiting purine biosynthesis enzyme, crucial component of the *de novo* synthesis of purine and pyrimidine nucleotides but also essential in the purine salvage pathway, which recycles the breakdown of nucleic acids for their synthesis. More than 25 pathogenic mutations in *PRPS1* have been found in human diseases. In leukemia, these mutations lead to constitutive purine biosynthesis, accumulation of purine nucleotides inside the cells and drug resistance. Experimental studies showed that *PRPS1*-mutant cells have an increased synthesis of inosine monophosphate metabolites that competitively inhibit the conversion of thiopurines into 6-MP (active metabolites) [111,112]. Gain-of-function mutations and increased levels of PRPS1 could also facilitate the conversion of 5-Fluorouracil (5-FU) (a pyrimidine analog used for several types of cancers) to their active metabolites (fluorodeoxyuridine monophosphate, fluorodeoxyuridine triphosphate and fluorouridine triphosphate), subsequently triggering genomic damage and apoptosis [113]. Therefore, ALL patients who carry activating mutations could benefit from 5-FU administration during therapy [100]. Whole exome sequencing analysis revealed *PRPS1* mutations in 2.7% and 13% of relapsed B-ALL cases from Germany and China, respectively, being p.Ala190Thr and p.Ser103Thr the most common. All patients carrying *PRPS1* mutations had early relapse during treatment and poor prognosis [111]. Furthermore, increased expression of *PRPS1* has been associated with high white blood cell count, positive MRD and higher risk for relapse [99]. These studies underline the importance of *PRPS1* as a novel therapeutic target in ALL treatment.

Targeted B-lineage receptor genes in relapsed/refractory ALL

The lineage-specific surface molecules like CD19, CD20 and CD22 are several targets of the current approaches for relapsed/refractory ALL [114]. These cell surface molecules are found in the majority of B-lineage leukemias and lymphomas [115–117]. Along with CD19 and prior to the expression of CD20, CD22 is detected at B-cell differentiation earliest stages [118]. Today, these molecules are considered potential targets of pharmaceutical companies, research organizations and clinical trials to develop new therapies that target tumor cells at both the cellular and genetic levels. Two examples of these therapies are the antibody-based drugs and chimeric antigen receptor T-cells (CAR T cells) therapy, which are opening a new era of hematological cancers treatment, especially for NCI high-risk groups, adolescents and young adults (AYAs) ALL [119–121].

CD19

The CD19 antigen is the most ubiquitously expressed marker in B-cells. CD19 expression initiates during B-lineage commitment from hematopoietic stem cells, continuing along the B-cell differentiation process until its down-regulation in the plasma cell stage [122]. Due to their differentiation arrest, CD19 expression is maintained, and commonly up-regulated, in B-lymphoid leukemias and lymphomas [123]. Based on this knowledge, treatment targeting CD19 have been developed and two of them are approved by the FDA, blinatumomab and tisagenlecleucel (CAR T-cell therapy) (Fig. 3) [120,121].

Blinatumomab is a type of immunotherapy treatment for relapsed/refractory and MRD+ precursor B-cell ALL. It consists in a chimeric T-cell-engaging (BiTE) antibody designed to redirect cytotoxic T-cells for lysis of the target cell [124,125]. Blinatumomab has two antibody arms, one anti-CD19 directed to B-lymphoblasts and one anti-CD3 that engages the T-cells, leading to activation and proliferation of T-cells and inducing apoptosis of B-lymphoblasts [126,127]. Blinatumomab has proven efficacy in adults, and in recent years it has also been evaluated in children and AYAs [120,128–133]. As many immunotherapy approaches, a downside of blinatumomab is the selection of CD19-negative leukemic clones and therapy resistance as a result. Combination of blinatumomab with second- or third-generation TKIs can overcome resistance by targeting CD19-negative *BCR-ABL1*+ clones [134,135]. These results look promising so far, but larger-scale clinical trials are needed to test the incorporation of blinatumomab in children with relapse/refractory ALL, children with persistent MRD and for patients who do not tolerate well the cytotoxic therapies [136,137].

Tisagenlecleucel (CTL019), also targeting CD19, is a CAR T-cells therapy approved by FDA in 2017 to treat diffuse large B-cell lymphoma, and refractory, second and later relapsed ALL (Fig. 3). Tisagenlecleucel induces a cytotoxic response of T-cells and complete remission rates as high as 80% can be achieved in children and AYAs B-ALL [120,121,127]. In fact, patients with unfavorable genetic features have reached good remission rates when treated with tisagenlecleucel, and these remission rates are even comparable to cases with good-prognosis genetics [138]. The main obstacles of CAR-T cells therapy include the development of cytokine release syndrome, infections, neurological toxicities, and its high cost of manufacture since it is individualized for each patient [139].

CD22

Most immunotherapy drugs were designed for patients with persistent disease, either as MRD positivity, intolerance to cytotoxic chemotherapy and unsuccessful remission. Inotuzumab/ozogamicin (InO) is a monoclonal anti-CD22 antibody linked to calicheamicin approved for adults with relapse/refractory B-ALL [140,141]. InO efficacy in adults is proven, but studies in childhood and AYAs ALL are still lacking. The first study in children showed complete remission rates in 67% of patients, irrespective of genetic subtype or prior treatment [142]. A recent phase II trial from Children's Oncology Group Protocol (AALL1621) reported a complete response in 58% of children and AYAs with relapse/refractory CD22+ B-ALL, and 65.4% of InO responders achieved MRD levels below 0.01% [143]. InO is generally well tolerated at the same doses as adults and clinical outcome has been outstanding so far, even for children with multiple relapses who did not respond to other therapeutic approaches [144].

Other pharmacogenes as future possibilities in the field of ALL treatment

The complex genomic and epigenomic background of ALL and the numerous factors involved in leukemogenesis and relapse exhibit the difficult pathways towards the identification of new therapeutic targets for ALL. Advances in treatment of other hematological diseases (as myeloid leukemia and lymphomas) and solid tumors have increased our

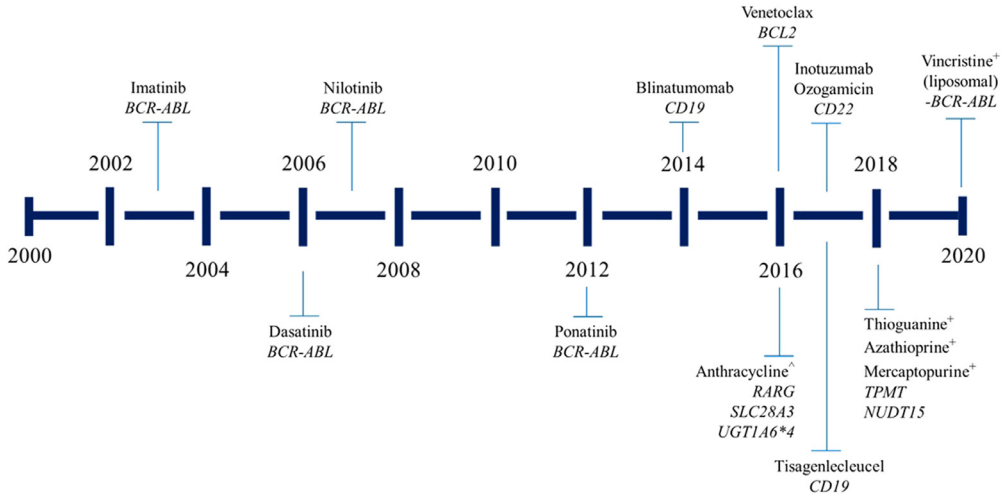

Fig. 3. Timeline of the FDA-approved drugs where a genetic testing is required before its prescription. ^Pharmacogenes consideration published in the guidelines by Canadian Pharmacogenomics Network for Drug Safety; +Pharmacogenomic biomarkers in drug labeling for chemotherapeutic agents developed before the 60 s; FDA: U.S. Food & Drug Administration.

possibilities to treat ALL. As example, it has been reported that certain mutations in the granulocyte colony stimulating factor (G-CSF) gene significantly reduce the anti-leukemic potential after ibrutinib treatment, a Bruton's tyrosine kinase (BTK) inhibitor (FDA-approved) [145–147]. BTK has been found abnormally expressed in ALL [148,149] and pre-B cells have shown high sensitivity to ibrutinib in preclinical models of B-ALL [148]. Other example is survivin, an apoptosis inhibitor and cell cycle regulator that is expressed in many types of tumors (including ALL) and is associated with chemoresistance [150,151]. Several clinical trials have found survivin as a therapeutic target to ALL [152–154]. In the same way, the *BCL-2* gene is another example of a potential pharmacogene in ALL. This gene was initially discovered as relevant in the pathogenesis of follicular lymphoma, and as a contributor to the pathophysiology of diverse hematological malignancies. Based on observations derived from acute myeloid leukemia and chronic lymphocytic leukemia with 17p deletions and p53 mutations [155], the use of inhibitors of the anti-apoptotic protein BCL-2 (Venetoclax) to treat ALL subtypes carrying p53 deletions (as hypodiploid ALL that has a dismal prognosis) is currently undergoing [156–158]. Venetoclax plus chemotherapy is exhibiting good efficacy in adult refractory/relapsed T-ALL [159]. Additionally, preclinical studies have shown remarkable effectivity in childhood B-ALL [160] and the first phase I trials are currently developing, with encouraging results (NCT03181126) [161].

Available genetic tests and drugs to optimize therapy in ALL

Before the 1960s, monochemotherapy protocols were used for all patients with ALL, but it was an incurable disease. Aminopterin (1948) followed by pituitary adrenocorticotropic hormone (1950), prednisone (1950), and mercaptopurine (1953) were the first chemotherapy agents used in ALL treatment, however the mortality rate was 100% [162–164]. During the 60 s, the effectiveness of a combination of anti-leukemic agents (including vincristine, asparaginase, daunorubicin, cytarabine, and etoposide) in the induction and maintenance of remission in children with acute leukemias was demonstrated. Treatment based on a combination of these drugs reached 50% of remission; nevertheless, all patients still relapsed [165,166]. After that, the implementation of risk-adapted therapies, which included agents FDA-approved and that were developed during the 50 s and 60 s, improved considerably the remission and OS (approx. 50%) rates [167].

Precision or personalized medicine, which has shown an outstanding development after the human genome sequencing, is considered a therapeutic approach that takes into consideration the individual needs of patients based on their genetic, biomarker, phenotype, or psychosocial characteristics. This kind of medicine distinguishes each individual from other patients with similar clinical presentations, in order to provide therapy that is best suited for each patients' condition [168]. Precision medicine also identifies genetic variants or mutations that could specifically influence treatment response either to increase their OS and to minimize the negative effects during treatment [169]. Studies conducted in ALL to identify useful genetic variants to optimize drug therapy have provided enough evidence on their clinical utility for *BCR-ABL, TPMT, NUDT15, RARG,* SLC28A3, and *UGT1A6*4*. In fact, FDA has approved their genotyping as routine clinical analysis before specific drugs administration [42,45,49,170,171]. Table 1 enlists FDA approved test in ALL and Fig. 3 displays a timeline of the FDA-approved drugs where a genetic testing is required before its prescription [172].

Conclusions

Genomic approaches in cancer research were a turning point in precision medicine. Not only it gave us a greater insight of the biological mechanisms involved in cancer development, progression and recurrence, but also we have been able to find new ways to treat ALL patients, to develop targeted therapies and to design a more efficient classification system. Nevertheless, ALL still represents a challenge in low- and middle-income countries, where high rates of relapse and death have been reported. The promise of precision medicine to assign a treatment based on the genetic background of each patient at most, or for specific populations at least, is still a challenging task. Great progress has been made, nevertheless, precision medicine is not yet part of the daily care for patient. Therefore, it is necessary to bring this knowledge from the bench to the clinic and translate the newest findings in health improvement of ALL patients.

Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Diego Alberto Bárcenas-López: Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Diana Karen Mendiola-Soto:** Data curation, Writing - original draft. **Juan Carlos Núñez-Enríquez:** Writing - review & editing. **Juan Manuel Mejía-Aranguré:** Writing - review & editing. **Alfredo Hidalgo-Miranda:** Writing - review & editing. **Silvia Jiménez-Morales:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

Table 1
Examples of pharmacogenetics test in acute lymphoblastic leukemia approved by the Food and Drug Administration.

Gene	Variant	Biological effect	Drug	Clinical Efect	PGx Label
BCR-ABL1	Chimeric oncogenic gene	Constitutively activated tyrosine kinase. Causes anomalous activation of intracellular signal transduction pathways, leading to an unstable genome, abnormal cellular proliferation, and amplification of leukemia clones.	Tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib)	Treatment response	Testing for ALL, as well to AML and CML cases at diagnosis and in positive patients under relapse.
RARG	rs2229774	Reduced repression of the key ACT genetic determinant.	Anthracycline	Cardiotoxicity risk (ACT)	Testing should be performed in ALL children treated with doxorubicin or daunorubicin.
SLC28A3	rs7853758	Reduced SLC28A3 mRNA expression in monocytes.			
*UGT1A6*4*	rs17863783	30–100% reduction in enzyme activity.			
TPMT	rs1800462 rs1800460 rs1142345	Low enzyme activity.	Thiopurine (Thioguanine)	Myelosuppression high risk	Patients treated with Thiopurines
NUDT15	rs116855232 rs147390019 rs186364861 rs869320766 rs766023281 K35E c.103A>*G* (no rsID) rs746071566	Loss-of-function of *NUDT15* and reduced degradation of active thiopurine nucleotide metabolites.			

CML: Chronic myeloid leukemia, AML: Acute myeloid leukemia, ALL: Acute Lymphoblastic Leukemia, ACT: Anthracycline-induced cardiotoxicity; PGx: pharmacogenomics/pharmacogenetics.

Acknowledgments

The authors thank Dr. Elva Jiménez-Hernández for her suggestions in the Figure 1 design. This work was supported by the Consejo Nacional de Ciencia y Tecnología (CONACyT, Investigación en Fronteras de la Ciencia (IFC)−2016–01–2119 and by the National Institute of Genomic Medicine (19/2019/I). Diego Alberto Bárcenas-López (Programa de Doctorado en Ciencias Biológicas, UNAM) and Diana Karen Mendiola-Soto (Doctorado en Ciencias Biomédicas, UNAM) were supported by CONACyT (CVU 737534 and 706961, respectively).

References

[1] L.L. Robison, S. Bhatia, Late-effects among survivors of leukaemia and lymphoma during childhood and adolescence, Br. J. Haematol. 122 (2003) 345–359, doi:10.1046/j.1365-2141.2003.04499.x.
[2] A. Medina-Sanson, Introduction: childhood Leukemia, in: J. Mejía-Aranguré (Ed.), Etiology of Acute Leukemias in Children, Springer, Cham, 2016, pp. 1–48, doi:10.1007/978-3-319-05798-9.
[3] Cancer Today. Data visualization tools for exploring the global cancer burden in 2018. https://gco.iarc.fr/today/home (accessed May 22, 2020).
[4] M.L. Pérez-Saldivar, A. Fajardo-Gutiérrez, R. Bernáldez-Ríos, A. Martínez-Avalos, A. Medina-Sanson, L. Espinosa-Hernández, Jde.D. Flores-Chapa, R. Amador-Sánchez, J.G. Peñaloza-González, F.J. Alvarez-Rodríguez, V. Bolea-Murga, J. Flores-Lujano, Mdel.C. Rodríguez-Zepeda, R. Rivera-Luna, E.M. Dorantes-Acosta, E. Jiménez-Hernández, M. Alvarado-Ibarra, M.M. Velázquez-Aviña, J.R. Torres-Nava, D.A. Duarte-Rodríguez, R. Paredes-Aguilera, Mde.L. Del Campo-Martínez, R. Cárdenas-Cardos, P.H. Alamilla-Galicia, V.C. Bekker-Méndez, M.C. Ortega-Alvarez, J.M. Mejia-Arangure, Childhood acute leukemias are frequent in Mexico city: descriptive epidemiology, BMC Cancer 11 (2011) 355, doi:10.1186/1471-2407-11-355.
[5] E. Jiménez-Hernández, E.Z. Jaimes-Reyes, J. Arellano-Galindo, X. García-Jiménez, H.M. Tiznado-García, M.T. Dueñas-González, O. Martínez-Villegas, B. Sánchez-Jara, V.C. Bekker-Méndez, M.G. Ortíz-Torres, A. Ortíz-Fernández, T. Marín-Palomares, J.M. Mejía-Aranguré, Survival of Mexican children with acute lymphoblastic leukaemia under treatment with the protocol from the Dana-Farber cancer institute 00-01, Biomed. Res. Int. 2015 (2015) 1–9, doi:10.1155/2015/576950.
[6] A. Bonaventure, R. Harewood, C.A. Stiller, G. Gatta, J. Clavel, D.C. Stefan, H. Carreira, D. Spika, R. Marcos-Gragera, R. Peris-Bonet, M. Piñeros, M. Sant, C.E. Kuehni, M. Murphy, M.P. Coleman, C. Allemani, CONCORD Working Group, Worldwide comparison of survival from childhood leukaemia for 1995–2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries, Lancet Haematol. 4 (2017) e202–e217, doi:10.1016/S2352-3026(17)30052-2.
[7] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, P. Hesseling, F. Moreno, H.Y. Shin, C.A. Stiller, International Incidence of Childhood Cancer, Volume III (electronic version), International Agency for Research on Cancer, Lyon, France, 2017 Available from: http://iicc.iarc.fr/results/ accessed [06/22/2020].
[8] S.P. Hunger, M.L. Loh, J.A. Whitlock, N.J. Winick, W.L. Carroll, M. Devidas, E.A. Raetz, COG Acute Lymphoblastic Leukemia Committee., Children's oncology group's 2013 blueprint for research: acute lymphoblastic leukemia, Pediatr. Blood Cancer 60 (2013) 957–963, doi:10.1002/pbc.24420.
[9] C.H. Pui, C.G. Mullighan, W.E. Evans, M.V. Relling, Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood 120 (2012) 1165–1174, doi:10.1182/blood-2012-05-378943.
[10] K.G. Roberts, C.G. Mullighan, Genomics in acute lymphoblastic leukaemia: insights and treatment implications, Nat. Rev. Clin. Oncol. 12 (2015) 344–357, doi:10.1038/nrclinonc.2015.38.
[11] J.M. Kahn, T.H. Keegan, L. Tao, R. Abrahão, A. Bleyer, A.D. Viny, Racial disparities in the survival of American children, adolescents, and young adults with acute lymphoblastic leukemia, acute myelogenous leukemia, and Hodgkin lymphoma, Cancer 122 (2016) 2723-;2730, doi:10.1002/cncr.30089.
[12] E. Quiroz, I. Aldoss, V. Pullarkat, E. Rego, G. Marcucci, D. Douer, The emerging story of acute lymphoblastic leukemia among the Latin American population - biological and clinical implications, Blood Rev. 33 (2019) 98–105, doi:10.1016/j.blre.2018.08.002.
[13] W.E. Evans, M.V. Relling, Pharmacogenomics: translating functional genomics into rational therapeutics, Science 286 (1999) 487–491, doi:10.1126/science.286.5439.487.
[14] C. Wu, W. Li, Genomics and pharmacogenomics of pediatric acute lymphoblastic leukemia, Crit. Rev. Oncol. Hematol. 126 (2018) 100–111, doi:10.1016/j.critrevonc.2018.04.002.
[15] N. Coccaro, L. Anelli, A. Zagaria, G. Specchia, F. Albano, Next-generation sequencing in acute lymphoblastic leukemia, Int. J. Mol. Sci. 20 (2019) 2929, doi:10.3390/ijms20122929.
[16] R.A. Larson, Chapter 91 acute lymphoblastic leukemia, in: K. Kausahnsky, W.J. Williams (Eds.), Williams Hematology, 9th edition, McGraw-Hill Medical, New York, 2016, pp. 1505–1526. EEUUISBN 978-0-07-183300-4.
[17] M. Kato, A. Manabe, Treatment and biology of pediatric acute lymphoblastic leukemia, Pediatr. Int. 60 (2018) 4–12, doi:10.1111/ped.13457.
[18] M. Talpaz, N.P. Shah, H. Kantarjian, N. Donato, J. Nicoll, R. Paquette, J. Cortes, S. O'Brien, C. Nicaise, E. Bleickardt, M.A. Blackwood-Chirchir, V. Iyer, T.T. Chen, F. Huang, A.P. Decillis, C.L. Sawyers, Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias, N. Engl. J. Med. 354 (2006) 2531–2541, doi:10.1056/NEJMoa055229.
[19] H. Inaba, M. Greaves, C.G. Mullighan, Acute lymphoblastic leukaemia, Lancet 381 (2013) 1943–1955, doi:10.1016/S0140-6736(12)62187-4.
[20] N. Kotur, L. Dokmanovic, D. Janic, B. Stankovic, N. Krstovski, N. Tosic, T. Katsila, G.P. Patrinos, B. Zukic, S. Pavlovic, TPMT gene expression is increased during maintenance therapy in childhood acute lymphoblastic leukemia patients in a TPMT gene promoter variable number of tandem repeat-dependent manner, Pharmacogenomics 16 (2015) 1701–1712, doi:10.2217/pgs.15.109.
[21] H.Y. Kim, S.H. Lee, M.N. Lee, J.W. Kim, Y.H. Kim, M.J. Kim, Y.M. Lee, B. Kang, Y.H. Choe, N.H. Lee, D.H. Kim, K.H. Yoo, K.W. Sung, S.Y. Lee, H.H. Koo, Complete sequence-based screening of TPMT variants in the Korean population, Pharmacogenet. Genom. 25 (2015) 143–146, doi:10.1097/FPC.0000000000000117.

[22] S. Rudin, M. Marable, R.S. Huang, The promise of pharmacogenomics in reducing toxicity during acute lymphoblastic leukemia maintenance treatment, Genom. Proteom. Bioinform. 15 (2017) 82–93, doi:10.1016/j.gpb.2016.11.003.

[23] T.W. Kouwenberg, B. van den Bosch, J. Bierau, D. Te Loo, M. Coenen, M.M. Hagleitner, Dosage of 6-mercaptopurine in relation to genetic TPMT and ITPA variants: toward individualized pediatric acute lymphoblastic leukemia maintenance treatment, J. Pediatr. Hematol. Oncol. 42 (2020) e94–e97, doi:10.1097/MPH.0000000000001707.

[24] M.V. Relling, E.E. Gardner, W.J. Sandborn, K. Schmiegelow, C.H. Pui, S.W. Yee, C.M. Stein, M. Carrillo, W.E. Evans, T.E. Klein, Clinical Pharmacogenetics Implementation Consortium, Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Version 2, Clin. Pharmacol. Ther. 89 (2011) 387–391, doi:10.1038/clpt.2010.320.

[25] H.V. Aráoz, K. D'Aloi, M.E. Foncuberta, C.G. Sanchez La Rosa, C.N. Alonso, L. Chertkoff, M. Felice, Pharmacogenetic studies in children with acute lymphoblastic leukemia in Argentina, Leuk. Lymphoma 56 (2015) 1370–1378, doi:10.3109/10428194.2014.951844.

[26] M. Levinsen, E.Ø. Rotevatn, S. Rosthøj, J. Nersting, J. Abrahamsson, M.L. Appell, S. Bergan, A.G. Bechensteen, A. Harila-Saari, M. Heyman, O.G. Jonsson, J.B. Maxild, M. Niemi, S. Söderhäll, K. Schmiegelow, Pharmacogenetically based dosing of thiopurines in childhood acute lymphoblastic leukemia: influence on cure rates and risk of second cancer, Pediatr. Blood Cancer 61 (2014) 797–802, doi:10.1002/pbc.24921.

[27] S.K. Yang, M. Hong, J. Baek, H. Choi, W. Zhao, Y. Jung, T. Haritunians, B.D. Ye, K.J. Kim, S.H. Park, S.K. Park, D.H. Yang, M. Dubinsky, I. Lee, D.P. McGovern, J. Liu, K. Song, A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia, Nat. Genet. 46 (2014) 1017–1020, doi:10.1038/ng.3060.

[28] T. Moriyama, R. Nishii, V. Perez-Andreu, W. Yang, F.A. Klussmann, X. Zhao, T.N. Lin, K. Hoshitsuki, J. Nersting, K. Kihira, U. Hofmann, Y. Komada, M. Kato, R. McCorkle, L. Li, K. Koh, C.R. Najera, S.K. Kham, T. Isobe, Z. Chen, E.K. Chiew, D. Bhojwani, C. Jeffries, Y. Lu, M. Schwab, H. Inaba, C.H. Pui, M.V. Relling, A. Manabe, H. Hori, K. Schmiegelow, A.E. Yeoh, W.E. Evans, J.J. Yang, NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity, Nat. Genet. 48 (2016) 367–373, doi:10.1038/ng.3508.

[29] T. Moriyama, Y.L. Yang, R. Nishii, H. Ariffin, C. Liu, T.N. Lin, W. Yang, D.T. Lin, C.H. Yu, S. Kham, C.H. Pui, W.E. Evans, S. Jeha, M.V. Relling, A.E. Yeoh, J.J. Yang, Novel variants in NUDT15 and thiopurine intolerance in children with acute lymphoblastic leukemia from diverse ancestry, Blood 130 (2017) 1209–1212, doi:10.1182/blood-2017-05-782383.

[30] D. Yin, X. Xia, J. Zhang, S. Zhang, F. Liao, G. Zhang, Y. Zhang, Q. Hou, X. Yang, H. Wang, Z. Ma, H. Wang, Y. Zhu, W. Zhang, Y. Wang, B. Liu, L. Wang, H. Xu, Y. Shu, Impact of NUDT15 polymorphisms on thiopurines-induced myelotoxicity and thiopurines tolerance dose, Oncotarget 8 (2017) 13575–13585, doi:10.18632/oncotarget.14594.

[31] D.C. Liang, C.P. Yang, H.C. Liu, T.H. Jaing, S.H. Chen, I.J. Hung, T.C. Yeh, T.H. Lin, C.L. Lai, C.Y. Lai, L.Y. Shih, NUDT15 gene polymorphism related to mercaptopurine intolerance in Taiwan Chinese children with acute lymphoblastic leukemia, Pharmacogenomics J. 16 (2016) 536–539, doi:10.1038/tpj.2015.75.

[32] J.J. Yang, W. Landier, W. Yang, C. Liu, L. Hageman, C. Cheng, D. Pei, Y. Chen, K.R. Crews, N. Kornegay, F.L. Wong, W.E. Evans, C.H. Pui, S. Bhatia, M.V. Relling, Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia, J. Clin. Oncol. 33 (2015) 1235–1242, doi:10.1200/JCO.2014.59.4671.

[33] H. Suzuki, H. Fukushima, R. Suzuki, S. Hosaka, Y. Yamaki, C. Kobayashi, A. Sakai, K. Imagawa, A. Iwabuchi, A. Yoshimi, T. Nakao, K. Kato, M. Tsuchida, N. Kiyokawa, K. Koike, E. Noguchi, T. Fukushima, R. Sumazaki, Genotyping NUDT15 can predict the dose reduction of 6-MP for children with acute lymphoblastic leukemia especially at a preschool age, J. Hum. Genet. 61 (2016) 797–801, doi:10.1038/jhg.2016.55.

[34] Y. Tanaka, H. Nakadate, K. Kondoh, K. Nakamura, K. Koh, A. Manabe, Interaction between NUDT15 and ABCC4 variants enhances intolerability of 6-mercaptopurine in Japanese patients with childhood acute lymphoblastic leukemia, Pharmacogenomics J. 18 (2018) 275–280, doi:10.1038/tpj.2017.12.

[35] P. Chambon, A decade of molecular biology of retinoic acid receptors, FASEB J. 10 (1996) 940–954 doi.org/, doi:10.1096/fasebj.10.9.8801176.

[36] Q. Tang, Y. Chen, C. Meyer, T. Geistlinger, M. Lupien, Q. Wang, T. Liu, Y. Zhang, M. Brown, X.S. Liu, A comprehensive view of nuclear receptor cancer cistromes, Cancer Res. 71 (2011) 6940–6947, doi:10.1158/0008-5472.CAN-11-2091.

[37] M.R. Conserva, I. Redavid, L. Anelli, A. Zagaria, G. Specchia, F. Albano, RARG gene dysregulation in acute myeloid leukemia, Front. Mol. Biosci. 6 (2019) 114, doi:10.3389/fmolb.2019.00114.

[38] G.D. Salvo, F. D'Aiello, F.D. Gaizo, P. Indolfi, F. Casale, M.T. di Tullio, D. Iarussi, R. Calabrò, M.G. Russo, Early detection of anthracycline-induced cardiotoxicity in long-term survivors of acute lymphoblastic leukemia treated with low cumulative dose, J. Cardiovasc. Echogr. 24 (1) (2014) 25–28, doi:10.4103/2211-4122.132282.

[39] D. Chellapandian, J.D. Pole, P.C. Nathan, L. Sung, Congestive heart failure among children with acute leukemia: a population-based matched cohort study, Leuk. Lymphoma 60 (2) (2019) 385–394, doi:10.1080/10428194.2018.1474522.

[40] F. Aminkeng, A.P. Bhavsar, H. Visscher, S.R. Rassekh, Y. Li, J.W. Lee, L.R. Brunham, H.N. Caron, E.C. van Dalen, L.C. Kremer, H.J. van der Pal, U. Amstutz, M.J. Rieder, D. Bernstein, B.C. Carleton, M.R. Hayden, C.J. Ross, A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer, Nat. Genet. 47 (2015) 1079–1084, doi:10.1038/ng.3374.

[41] G. Minotti, P. Menna, E. Salvatorelli, G. Cairo, L. Gianni, Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity, Pharmacol. Rev. 56 (2004) 185–229, doi:10.1124/pr.56.2.6.

[42] F. Aminkeng, C.J.D. Ross, S.R. Rassekh, S. Hwang, M.J. Rieder, A.P. Bhavsar, A. Smith, S. Sanatani, K.A. Gelmon, D. Bernstein, M.R. Hayden, U. Amstutz, B.C. Carleton, C.P.N.D.S. Clinical Practice Recommendations Group, Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity, Br. J. Clin. Pharmacol. 82 (2016) 683–695, doi:10.1111/bcp.13008.

[43] J.H. Gray, R.P. Owen, K.M. Giacomini, The concentrative nucleoside transporter family, SLC28, Pflug. Arch. 447 (2004) 728–734, doi:10.1007/s00424-003-1107-y.

[44] J.C. Sági, B. Egyed, A. Kelemen, N. Kutszegi, M. Hegyi, A. Gézsi, M.A. Herlitschke, A. Rzepiel, L.E. Fodor, G. Ottóffy, G.T. Kovács, D.J. Erdélyi, C. Szalai, Á.F. Semsei, Possible roles of genetic variations in chemotherapy related cardiotoxicity in pediatric acute lymphoblastic leukemia and osteosarcoma, BMC Cancer 18 (1) (2018) 704, doi:10.1186/s12885-018-4629-6.

[45] H. Visscher, C.J. Ross, S.R. Rassekh, A. Barhdadi, M.P. Dubé, H. Al-Saloos, G.S. Sandor, H.N. Caron, E.C. van Dalen, L.C. Kremer, H.J. van der Pal, A.M. Brown, P.C. Rogers, M.S. Phillips, M.J. Rieder, B.C. Carleton, M.R. Hayden, Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children, J. Clin. Oncol. 30 (2012) 1422–1428, doi:10.1200/JCO.2010.34.3467.

[46] H. Visscher, C.J. Ross, S.R. Rassekh, G.S. Sandor, H.N. Caron, E.C. van Dalen, L.C. Kremer, H.J. van der Pal, P.C. Rogers, M.J. Rieder, B.C. Carleton, M.R. Hayden, CPNDS Consortium, Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of anthracycline-induced cardiotoxicity in children, Pediatr. Blood Cancer. 60 (2013) 1375–1381, doi:10.1002/pbc.24505.

[47] T. Zeller, P. Wild, S. Szymczak, M. Rotival, A. Schillert, R. Castagne, S. Maouche, M. Germain, K. Lackner, H. Rossmann, M. Eleftheriadis, C.R. Sinning, R.B. Schnabel, E. Lubos, D. Mennerich, W. Rust, C. Perret, C. Proust, V. Nicaud, J. Loscalzo, N. Hübner, D. Tregouet, T. Münzel, A. Ziegler, L. Tiret, S. Blankenberg, F. Cambien, Genetics and beyond: the transcriptome of human monocytes and disease susceptibility, PLoS One 5 (2010) e10693, doi:10.1371/journal.pone.0010693.

[48] R.H. Tukey, C.P. Strassburg, Human UDP-glucuronosyltransferases: metabolism, expression, and disease, Annu. Rev. Pharmacol. Toxicol. 40 (2000) 581–616, doi:10.1146/annurev.pharmtox.40.1.581.

[49] S. Krishnaswamy, Q. Hao, A. Al-Rohaimi, L.M. Hesse, L.L. von Moltke, D.J. Greenblatt, M.H. Court, UDP glucuronosyltransferase (UGT) 1A6 pharmacogenetics: II. Functional impact of the three most common nonsynonymous UGT1A6 polymorphisms (S7A, T181A, and R184S), J. Pharmacol. Exp. Ther. 313 (2005) 1340–1346, doi:10.1124/jpet.104.081968.

[50] Q. Gong, J.W. Cho, T. Huang, C. Potter, N. Gholami, N.K. Basu, S. Kubota, S. Carvalho, M.W. Pennington, I.S. Owens, N.C. Popescu, Thirteen UDPglucuronosyltransferase genes are encoded at the human UGT1 gene complex locus, Pharmacogenetics 11 (2001) 357–368, doi:10.1097/00008571-200106000-00011.

[51] S. Nagar, J.J. Zalatoris, R.L. Blanchard, Human UGT1A6 pharmacogenetics: identification of a novel SNP, characterization of allele frequencies and functional analysis of recombinant allozymes in human liver tissue and in cultured cells, Pharmacogenetics 14 (2004) 487–499, doi:10.1097/01.fpc.0000114771.78957.cb.

[52] V.Y. Chang, J.J. Wang, Pharmacogenetics of chemotherapy-induced cardiotoxicity, Curr. Oncol. Rep. 20 (2018) 52, doi:10.1007/s11912-018-0696-8.

[53] R.G. Tirona, B.F. Leake, G. Merino, R.B. Kim, Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans, J. Biol. Chem. 276 (2001) 35669–35675, doi:10.1074/jbc.M103792200.

[54] M. Niemi, M.K. Pasanen, P.J. Neuvonen, Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake, Pharmacol. Rev. 63 (2011) 157–181, doi:10.1124/pr.110.002857.

[55] İ. Eldem, D. Yavuz, Ö. Cumaoğullari, T. İleri, E. Ünal İnce, M. Ertem, B. Doğanay Erdoğan, R. Bindak, H. Özdağ, N.L. Şatiroğlu-Tufan, L.Z. Uysal, SLCO1B1 Polymorphisms are associated with drug intolerance in childhood leukemia maintenance therapy, J. Pediatr. Hematol. Oncol. 40 (2018) e289–e294, doi:10.1097/MPH.0000000000001153.

[56] L.R. Treviño, N. Shimasaki, W. Yang, J.C. Panetta, C. Cheng, D. Pei, D. Chan, A. Sparreboom, K.M. Giacomini, C.H. Pui, W.E. Evans, M.V. Relling, Germline genetic variation in an organic anion transporter polypeptide associated with methotrexate pharmacokinetics and clinical effects, J. Clin. Oncol. 27 (2009) 5972–5978, doi:10.1200/JCO.2008.20.4156.

[57] S. Radtke, O. Zolk, B. Renner, M. Paulides, M. Zimmermann, A. Möricke, M. Stanulla, M. Schrappe, T. Langer, Germline genetic variations in methotrexate candidate genes are associated with pharmacokinetics, toxicity, and outcome in childhood acute lymphoblastic leukemia, Blood 121 (2013) 5145–5153, doi:10.1182/blood-2013-01-480335.

[58] L.B. Ramsey, J.C. Panetta, C. Smith, W. Yang, Y. Fan, N.J. Winick, P.L. Martin, C. Cheng, M. Devidas, C.H. Pui, W.E. Evans, S.P. Hunger, M. Loh, M.V. Relling, Genome-wide study of methotrexate clearance replicates SLCO1B1, Blood 121 (2013) 898–904, doi:10.1182/blood-2012-08-452839.

[59] S.G. Liu, C. Gao, R.D. Zhang, X.X. Zhao, L. Cui, W.J. Li, Z.P. Chen, Z.X. Yue, Y.Y. Zhang, M.Y. Wu, J.X. Wang, Z.G. Li, H.Y. Zheng, Polymorphisms in methotrexate transporters and their relationship to plasma methotrexate levels, toxicity of high-dose methotrexate, and outcome of pediatric acute lymphoblastic leukemia, Oncotarget 8 (2017) 37761–37772, doi:10.18632/oncotarget.17781.

[60] S. Rudin, M. Marable, R.S. Huang, The promise of pharmacogenomics in reducing toxicity during acute lymphoblastic leukemia maintenance treatment, Genom. Proteom. Bioinform. 15 (2017) 82–93, doi:10.1016/j.gpb.2016.11.003.

[61] Q.Q. Song, W.Y. Xie, Y.J. Tang, J. Zhang, J. Liu, Genetic variation in the glucocorticoid pathway involved in interindividual differences in the glucocorticoid treatment, Pharmacogenomics 18 (2017) 293–316, doi:10.2217/pgs-2016-0151.

[62] M.A. Pufall, Glucocorticoids and cancer, Adv. Exp. Med. Biol. 872 (2015) 315–333, doi:10.1007/978-1-4939-2895-8_14.

[63] F.F. Quddus, B.G. Leventhal, J.M. Boyett, D.J. Pullen, W.M. Crist, M.J. Borowitz, Glucocorticoid receptors in immunological subtypes of childhood acute lymphocytic leukemia cells: a pediatric oncology group study, Cancer Res. 45 (1985) 6482–6486 PMID:3864532 .

[64] E. Buentke, A. Nordström, H. Lin, A.C. Björklund, E. Laane, M. Harada, L. Lu, T. Tegnebratt, S. Stone-Elander, M. Heyman, S. Söderhäll, A. Porwit, C.G. Ostenson, M. Shoshan, K.P. Tamm, D. Grandér, Glucocorticoid-induced cell death is mediated through reduced glucose metabolism in lymphoid leukemia cells, Blood Cancer J. 1 (2011) e31, doi:10.1038/bcj.2011.27.

[65] W.J. Tissing, M.L. den Boer, J.P. Meijerink, R.X. Menezes, S. Swagemakers, P.J. van der Spek, S.E. Sallan, S.A. Armstrong, R. Pieters, Genomewide identification of prednisolone-responsive genes in acute lymphoblastic leukemia cells, Blood 109 (2007) 3929–3935, doi:10.1182/blood-2006-11-056366.

[66] I. Fleury, M. Primeau, A. Doreau, I. Costea, A. Moghrabi, D. Sinnett, M. Krajinovic, Polymorphisms in genes involved in the corticosteroid response and the outcome of childhood acute lymphoblastic leukemia, Am. J. Pharmacogenomics 4 (2004) 331–341, doi:10.2165/00129785-200404050-00006.

[67] E. Cuzzoni, S. De Iudicibus, F. Bartoli, A. Ventura, G. Decorti, Association between BclI polymorphism in the NR3C1 gene and *in vitro* individual variations in lymphocyte responses to methylprednisolone, Br. J. Clin. Pharmacol. 73 (2012) 651–655, doi:10.1111/j.1365-2125.2011.04130.x.

[68] O.T. Eipel, K. Németh, D. Török, K. Csordás, M. Hegyi, A. Ponyi, A. Ferenczy, D.J. Erdélyi, M. Csóka, G.T. Kovács, The glucocorticoid receptor gene polymorphism N363S predisposes to more severe toxic side effects during pediatric acute lymphoblastic leukemia (ALL) therapy, Int. J. Hematol. 97 (2) (2013) 216–222, doi:10.1007/s12185-012-1236-1.

[69] M. Labuda, A. Gahier, V. Gagné, A. Moghrabi, D. Sinnett, M. Krajinovic, Polymorphisms in glucocorticoid receptor gene and the outcome of childhood acute lymphoblastic leukemia (ALL), Leuk. Res. 34 (2010) 492–497, doi:10.1016/j.leukres.2009.08.007.

[70] R. El-Fayoumi, M. Hagras, A. Abozenadaha, W. Bawazir, T. Shinawi, Association between NR3C1 gene polymorphisms and toxicity induced by glucocorticoids therapy in Saudi children with acute lymphoblastic leukemia, Asian. Pac. J. Cancer. Prev. 19 (2018) 1415–1423 2018, doi:10.22034/APJCP.2018.19.5.1415.

[71] M. Kaymak Cihan, H.G. Karabulut, N. Yürür Kutlay, H. Ilgın Ruhi, A. Tükün, L. Olcay, Association between N363S and BclI polymorphisms of the glucocorticoid receptor gene (NR3C1) and glucocorticoid side effects during childhood acute lymphoblastic leukemia treatment. Glukokortikoid reseptör geninin (NR3C1) N363S ve BclI Polimorfizmleri ile Çocukluk Çağı Akut Lenfoblastik Lösemi Tedavisi Sırasında Görülen Glukokortikoid Yan Etkileri Arasındaki İlişki, Turk. J. Haematol. Off. J. Turk. Soc. Haematol. 34 (2) (2017) 151–158, doi:10.4274/tjh.2016.0253.

[72] L. Kuster, R. Grausenburger, G. Fuka, U. Kaindl, G. Krapf, A. Inthal, G. Mann, M. Kauer, J. Rainer, R. Kofler, A. Hall, M. Metzler, L.H. Meyer, C. Meyer, J. Harbott, R. Marschalek, S. Strehl, O.A. Haas, R. Panzer-Grümayer, ETV6/RUNX1-positive relapses evolve from an ancestral clone and frequently acquire deletions of genes implicated in glucocorticoid signaling, Blood 117 (2011) 2658–2667, doi:10.1182/blood-2010-03-275347.

[73] H. Xiao, L.M. Wang, Y. Luo, X. Lai, C. Li, J. Shi, Y. Tan, S. Fu, Y. Wang, N. Zhu, J. He, W. Zheng, X. Yu, Z. Cai, H. Huang, Mutations in epigenetic regulators are involved in acute lymphoblastic leukemia relapse following allogeneic hematopoietic stem cell transplantation, Oncotarget 7 (2016) 2696–2708, doi:10.18632/oncotarget.6259.

[74] R. Grausenburger, S. Bastelberger, C. Eckert, M. Kauer, M. Stanulla, C. Frech, E. Bauer, D. Stoiber, A. von Stackelberg, A. Attarbaschi, O.A. Haas, R. Panzer-Grümayer, Genetic alterations in glucocorticoid signaling pathway components are associated with adverse prognosis in children with relapsed ETV6/RUNX1-positive acute lymphoblastic leukemia, Leuk. Lymphoma 57 (2016) 1163–1173, doi:10.3109/10428194.2015.1088650.

[75] H. Xiao, Y. Ding, Y. Gao, L.M. Wang, H. Wang, L. Ding, X. Li, X. Yu, H. Huang, Haploinsufficiency of NR3C1 drives glucocorticoid resistance in adult acute lymphoblastic leukemia cells by down-regulating the mitochondrial apoptosis axis, and is sensitive to Bcl-2 blockage, Cancer Cell Int. 19 (2019) 218, doi:10.1186/s12935-019-0940-9.

[76] A. Hamidovic, K. Hahn, J. Kolesar, Clinical significance of ABCB1 genotyping in oncology, J. Oncol. Pharm. Pract. 16 (2010) 39–44, doi:10.1177/1078155209104380.

[77] J. Gregers, H. Gréen, I.J. Christensen, K. Dalhoff, H. Schroeder, N. Carlsen, S. Rosthoej, B. Lausen, K. Schmiegelow, C. Peterson, Polymorphisms in the ABCB1 gene and effect on outcome and toxicity in childhood acute lymphoblastic leukemia, Pharmacogenomics J. 15 (2015) 372–379, doi:10.1038/tpj.2014.81.

[78] X. Liu, ABC family transporters, in: Drug Transporters in Drug Disposition, 1141, Springer, Singapore, 2019, pp. 13–100. Effects and Toxicity. Adv. Exp. Med. Biol.

[79] D. Wang, A.D. Johnson, A.C. Papp, D.L. Kroetz, W. Sadée, Multidrug resistance polypeptide 1 (MDR1, ABCB1) variant 3435C>T affects mRNA stability, Pharmacogenet. Genom. 15 (10) (2005) 693–704 PMID:16141795 .

[80] P. Song, J.K. Lamba, L. Zhang, E. Schuetz, N. Shukla, B. Meibohm, C.R. Yates, G2677T and C3435T genotype and haplotype are associated with hepatic ABCB1 (MDR1) expression, J. Clin. Pharmacol. 46 (3) (2006) 373–379, doi:10.1177/0091270005284387.

[81] C. Kimchi-Sarfaty, J.M. Oh, I.W. Kim, Z.E. Sauna, A.M. Calcagno, S.V. Ambudkar, M.M. Gottesman, A "silent" polymorphism in the MDR1 gene changes substrate specificity, Science 315 (5811) (2007) 525–528, doi:10.1126/science.1135308.

[82] M. Tamura, M. Kondo, M. Horio, M. Ando, H. Saito, M. Yamamoto, Y. Horio, Y. Hasegawa, Genetic polymorphisms of the adenosine triphosphate-binding cassette transporters (ABCG2, ABCB1) and gefitinib toxicity, Nagoya J. Med. Sci. 74 (2012) 133–140 PMID:22515119 .

[83] F. Ceppi, C. Langlois-Pelletier, V. Gagné, J. Rousseau, C. Ciolino, S. De Lorenzo, K.M. Kevin, D. Cijov, S.E. Sallan, L.B. Silverman, D. Neuberg, J.L. Kutok, D. Sinnett, C. Laverdière, M. Krajinovic, Polymorphisms of the vincristine pathway and response to treatment in children with childhood acute lymphoblastic leukemia, Pharmacogenomics 15 (2014) 1105–1116, doi:10.2217/pgs.14.68.

[84] L. Ma, L. Ruan, H. Liu, H. Yang, Y. Feng, ABCB1 C3435T polymorphism is associated with leukemia susceptibility: evidence from a meta-analysis, Onco Targets Ther. 8 (2015) 1009–1015, doi:10.2147/OTT.S82144.

[85] R.M. Talaat, M. Y K El-Kelliny, B.A. El-Akhras, R.M. Bakry, K.F. Riad, A.A. Guirgis, Association of C3435T, C1236T and C4125A polymorphisms of the MDR-1 gene in Egyptian children with acute lymphoblastic leukaemia, Asian Pac. J. Cancer Prev. 19 (9) (2018) 2535–2543, doi:10.22034/APJCP.2018.19.9.2535.

[86] C. Ramos-Peñafiel, I. Olarte-Carrillo, R. Cerón-Maldonado, E. Rozen-Fuller, J.J. Kassack-Ipiña, G. Meléndez-Mier, J. Collazo-Jaloma, A. Martínez-Tovar, Effect of metformin on the survival of patients with ALL who express high levels of the ABCB1 drug resistance gene, J. Transl. Med. 16 (2018) 245, doi:10.1186/s12967-018-1620-6.

[87] A. Biondi, M. Schrappe, P. De Lorenzo, A. Castor, G. Lucchini, V. Gandemer, R. Pieters, J. Stary, G. Escherich, M. Campbell, C.K. Li, A. Vora, M. Aricò, S. Röttgers, V. Saha, M.G. Valsecchi, Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study, Lancet Oncol. 13 (2012) 93645, doi:10.1016/S1470-2045(12)70377-7.

[88] K.R. Schultz, A. Carroll, N.A. Heerema, W.P. Bowman, A. Aledo, W.B. Slayton, H. Sather, M. Devidas, H.W. Zheng, S.M. Davies, P.S. Gaynon, M. Trigg, R. Rutledge, D. Jorstad, N. Winick, M.J. Borowitz, S.P. Hunger, W.L. Carroll, B. Camitta, Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: children's oncology group study AALL0031, Leukemia 28 (2014) 1467–1471, doi:10.1038/leu.2014.30.

[89] R.C. Harvey, C.G. Mullighan, I.M. Chen, W. Wharton, F.M. Mikhail, A.J. Carroll, H. Kang, W. Liu, K.K. Dobbin, M.A. Smith, W.L. Carroll, M. Devidas, W.P. Bowman, B.M. Camitta, G.H. Reaman, S.P. Hunger, J.R. Downing, C.L. Willman, Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia, Blood 115 (26) (2010) 5312–5321, doi:10.1182/blood-2009-09-245944.

[90] K.G. Roberts, Y. Li, D. Payne-Turner, R.C. Harvey, Y.L. Yang, D. Pei, K. McCastlain, L. Ding, C. Lu, G. Song, J. Ma, J. Becksfort, M. Rusch, S.C. Chen, J. Easton, J. Cheng, K. Boggs, N. Santiago-Morales, I. Iacobucci, R.S. Fulton, …, C.G. Mullighan, Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia, N. Engl. J. Med. 371 (11) (2014) 1005–1015, doi:10.1056/NEJMoa1403088.

[91] T.H. Tran, M.L. Loh, Ph-like acute lymphoblastic leukemia, Hematol. Am. Soc. Hematol. Educ. Program. 2016 (2016) 561–566, doi:10.1182/asheducation-2016.1.561.

[92] S.K. Tasian, A. Assad, D.S. Hunter, Y. Du, M.L. Loh, A phase 2 study of ruxolitinib with chemotherapy in children with Philadelphia chromosome-like acute lymphoblastic leukemia (INCB18424-269/AALL1521): dose-finding results from the part 1 safety phase, Blood 132 (Supplement 1) (2018) 555, doi:10.1182/blood-2018-99-110221.

[93] D. Jones, D. Thomas, C.C. Yin, S. O'Brien, J.E. Cortes, E. Jabbour, M. Breeden, F.J. Giles, W. Zhao, H.M. Kantarjian, Kinase domain point mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia emerge after therapy with BCR-ABL kinase inhibitors, Cancer 113 (2008) 985–994, doi:10.1002/cncr.23666.

[94] S. Soverini, E. Abruzzese, M. Bocchia, M. Bonifacio, S. Galimberti, A. Gozzini, A. Iurlo, L. Luciano, P. Pregno, G. Rosti, G. Saglio, F. Stagno, M. Tiribelli, P. Vigneri, G. Barosi, M. Breccia, Next-generation sequencing for BCR-ABL1 kinase domain mutation testing in patients with chronic myeloid leukemia: a position paper, J. Hematol. Oncol. 12 (2019) 131, doi:10.1186/s13045-019-0815-5.

[95] C.G. Mullighan, L.A. Phillips, X. Su, J. Ma, C.B. Miller, S.A. Shurtleff, J.R. Downing, Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia, Science 322 (2008) 1377–1380, doi:10.1126/science.1164266.

[96] D. Bhojwani, C.H. Pui, Relapsed childhood acute lymphoblastic leukaemia, Lancet Oncol. 14 (2013) e205–e217, doi:10.1016/S1470-2045(12)70580-6.

[97] X. Ma, M. Edmonson, D. Yergeau, D.M. Muzny, O.A. Hampton, M. Rusch, G. Song, J. Easton, R.C. Harvey, D.A. Wheeler, J. Ma, H. Doddapaneni, B. Vadodaria, G. Wu, P. Nagahawatte, W.L. Carroll, I.M. Chen, J.M. Gastier-Foster, M.V. Relling, M.A. Smith, M. Devidas, J.M. Guidry Auvil, J.R. Downing, M.L. Loh, C.L. Willman, D.S. Gerhard, C.G. Mullighan, S.P. Hunger, J. Zhang, Rise and fall of subclones from diagnosis to relapse in pediatric B-acute lymphoblastic leukaemia, Nat. Commun. 6 (2015) 6604, doi:10.1038/ncomms7604.

[98] B. Li, S.W. Brady, X. Ma, S. Shen, Y. Zhang, Y. Li, K. Szlachta, L. Dong, Y. Liu, F. Yang, N. Wang, D.A. Flasch, M.A. Myers, H.L. Mulder, L. Ding, Y. Liu, L. Tian, K. Hagiwara, K. Xu, X. Zhou, E. Sioson, T. Wang, L. Yang, J. Zhao, H. Zhang, Y. Shao, H. Sun, L. Sun, J. Cai, H.Y. Sun, T.N. Lin, L. Du, H. Li, M. Rusch, M.N. Edmonson, J. Easton, X. Zhu, J. Zhang, C. Cheng, B.J. Raphael, J. Tang, J.R. Downing, L.B. Alexandrov, B.S. Zhou, C.H. Pui, J. Yang, J. Zhang, Therapy-induced mutations drive the genomic landscape of relapsed acute lymphoblastic leukemia, Blood 135 (2020) 41–55, doi:10.1182/blood.2019002220.

[99] Y. Ma, X. An, X. Guan, Q. Kong, Y. Wang, P. Li, Y. Meng, Y. Cui, X. Wen, Y. Guo, Y. Shen, J. Yu, High expression of PRPS1 induces an anti-apoptotic effect in B-ALL cell lines and predicts an adverse prognosis in Chinese children with B-ALL, Oncol. Lett. 15 (2018) 4314–4322, doi:10.3892/ol.2018.7903.

[100] D. Wang, Y. Chen, H. Fang, L. Zheng, Y. Li, F. Yang, Y. Xu, L. Du, B.S. Zhou, H. Li, Increase of PRPP enhances chemosensitivity of PRPS1 mutant acute lym-

phoblastic leukemia cells to 5-Fluorouracil, J. Cell. Mol. Med. 22 (2018) 6202–6212, doi:10.1111/jcmm.13907.
[101] C. Gazziola, P. Ferraro, M. Moras, P. Reichard, V. Bianchi, Cytosolic high K(m) 5′-nucleotidase and 5′(3′)-deoxyribonucleotidase in substrate cycles involved in nucleotide metabolism, J. Biol. Chem. 276 (2001) 6185–6190, doi:10.1074/jbc.M007623200.
[102] J.A. Meyer, J. Wang, L.E. Hogan, J.J. Yang, S. Dandekar, J.P. Patel, Z. Tang, P. Zumbo, S. Li, J. Zavadil, R.L. Levine, T. Cardozo, S.P. Hunger, E.A. Raetz, W.E. Evans, D.J. Morrison, C.E. Mason, W.L. Carroll, Relapse-specific mutations in NT5C2 in childhood acute lymphoblastic leukemia, Nat. Genet. 45 (2013) 290–294, doi:10.1038/ng.2558.
[103] G. Tzoneva, A. Perez-Garcia, Z. Carpenter, H. Khiabanian, V. Tosello, M. Allegretta, E. Paietta, J. Racevskis, J.M. Rowe, M.S. Tallman, M. Paganin, G. Basso, J. Hof, R. Kirschner-Schwabe, T. Palomero, R. Rabadan, A. Ferrando, Activating mutations in the NT5C2 nucleotidase gene drive chemotherapy resistance in relapsed ALL, Nat. Med. 19 (2013) 368–371, doi:10.1038/nm.3078.
[104] A. Hnízda, M. Fábry, T. Moriyama, P. Pachl, M. Kugler, V. Brinsa, D.B. Ascher, W.L. Carroll, P. Novák, M. Žaliová, J. Trka, P. Řezáčová, J.J. Yang, V. Veverka, Relapsed acute lymphoblastic leukemia-specific mutations in NT5C2 cluster into hotspots driving intersubunit stimulation, Leukemia 32 (2018) 1393–1403, doi:10.1038/s41375-018-0073-5.
[105] P. Richter-Pechańska, J.B. Kunz, J. Hof, M. Zimmermann, T. Rausch, O.R. Bandapalli, E. Orlova, G. Scapinello, J.C. Sagi, M. Stanulla, M. Schrappe, G. Cario, R. Kirschner-Schwabe, C. Eckert, V. Benes, J.O. Korbel, M.U. Muckenthaler, A.E. Kulozik, Identification of a genetically defined ultra-high-risk group in relapsed pediatric T-lymphoblastic leukemia, Blood Cancer J. 7 (2017) e523, doi:10.1038/bcj.2017.3.
[106] M.J. Barz, J. Hof, S. Groeneveld-Krentz, J.W. Loh, A. Szymansky, K. Astrahantseff, A. von Stackelberg, H. Khiabanian, A.A. Ferrando, C. Eckert, R. Kirschner-Schwabe, Subclonal NT5C2 mutations are associated with poor outcomes after relapse of pediatric acute lymphoblastic leukemia, Blood 135 (2020) 921–933, doi:10.1182/blood.2019002499.
[107] C.L. Dieck, G. Tzoneva, F. Forouhar, Z. Carpenter, A. Ambesi-Impiombato, M. Sánchez-Martín, R. Kirschner-Schwabe, S. Lew, J. Seetharaman, L. Tong, A.A. Ferrando, Structure and mechanisms of NT5C2 mutations driving thiopurine resistance in relapsed lymphoblastic leukemia, Cancer Cell 34 (2018) 136–147, doi:10.1016/j.ccell.2018.06.003.
[108] A. Hnízda, J. Škerlová, M. Fábry, P. Pachl, M. Šinalová, L. Vrzal, P. Man, P. Novák, P. Řezáčová, V. Veverka, Oligomeric interface modulation causes misregulation of purine 5′-nucleotidase in relapsed leukemia, BMC Biol. 14 (2016) 91, doi:10.1186/s12915-016-0313-y.
[109] G. Tzoneva, C.L. Dieck, K. Oshima, A. Ambesi-Impiombato, M. Sánchez-Martín, C.J. Madubata, H. Khiabanian, J. Yu, E. Waanders, I. Iacobucci, M.L. Sulis, M. Kato, K. Koh, M. Paganin, G. Basso, J.M. Gastier-Foster, M.L. Loh, R. Kirschner-Schwabe, C.G. Mullighan, R. Rabadan, A.A. Ferrando, Clonal evolution mechanisms in NT5C2 mutant-relapsed acute lymphoblastic leukaemia, Nature 553 (2018) 511–514, doi:10.1038/nature25186.
[110] C.L. Dieck, A. Ferrando, Genetics and mechanisms of NT5C2-driven chemotherapy resistance in relapsed ALL, Blood 133 (2019) 2263–2268, doi:10.1182/blood-2019-01-852392.
[111] B. Li, H. Li, Y. Bai, R. Kirschner-Schwabe, J.J. Yang, Y. Chen, G. Lu, G. Tzoneva, X. Ma, T. Wu, W. Li, H. Lu, L. Ding, H. Liang, X. Huang, M. Yang, L. Jin, H. Kang, S. Chen, A. Du, S. Shen, J. Ding, H. Chen, J. Chen, A. von Stackelberg, L. Gu, J. Zhang, A. Ferrando, J. Tang, S. Wang, B.B. Zhou, Negative feedback-defective PRPS1 mutants drive thiopurine resistance in relapsed childhood ALL, Nat. Med. 21 (2015) 563–571, doi:10.1038/nm.3840.
[112] T. Li, L. Song, Y. Zhang, Y. Han, Z. Zhan, Z. Xv, Y. Li, Y. Tang, Y. Yang, S. Wang, S. Li, L. Zheng, Y. Li, Y. Gao, Molecular mechanism of c-Myc and PRPS1/2 against thiopurine resistance in Burkitt's lymphoma, J. Cell. Mol. Med. 24 (2020) 6704–6715, doi:10.1111/jcmm.15322.
[113] Y. Wei, P. Yang, S. Cao, L. Zhao, The combination of curcumin and 5-fluorouracil in cancer therapy, Arch. Pharm. Res. 41 (2018) 1–13, doi:10.1007/s12272-017-0979-x.
[114] H. Rafei, H.M. Kantarjian, E.J. Jabbour, Recent advances in the treatment of acute lymphoblastic leukemia, Leuk. Lymphoma 60 (2019) 2606–2621, doi:10.1080/10428194.2019.1605071.
[115] J.C. Núñez-Enríquez, D.A. Bárcenas-López, A. Hidalgo-Miranda, E. Jiménez-Hernández, V.C. Bekker-Méndez, J. Flores-Lujano, K.A. Solis-Labastida, G.B. Martínez-Morales, F. Sánchez-Muñoz, L.E. Espinoza-Hernández, M.M. Velázquez-Aviña, L.E. Merino-Pasaye, A.J. García Velázquez, M.L. Pérez-Saldívar, R. Mojica-Espinoza, J. Ramírez-Bello, S. Jiménez-Morales, J.M. Mejía-Aranguré, Gene expression profiling of acute lymphoblastic leukemia in children with very early relapse, Arch. Med. Res. 47 (2016) 644–655, doi:10.1016/j.arcmed.2016.12.005.
[116] Arriaga-Pizano, L., Ramírez-Ramírez, D., Prieto-Chávez, J., Pelayo, R., Ruiz-Argüelles, A., Ruiz-Delgado, G.J., Marín y López, R.A., 2019. Gac Med Mex, 155, 20–29. doi:10.24875/GMM.18004418.
[117] D.A. Arber, A. Orazi, R. Hasserjian, J. Thiele, M.J. Borowitz, M.M. Le Beau, C.D. Bloomfield, M. Cazzola, J.W. Vardiman, The 2016 revision to the world health organization classification of myeloid neoplasms and acute leukemia, Blood 127 (2016) 2391–2405, doi:10.1182/blood-2016-03-643544.
[118] Editor(s) F. Naeim, P.N. Rao, S.X. Song, R.T. Phan, Chapter 2: principles of Immunophenotyping, in: F. Naeim, P.N. Rao, S.X. Song, R.T. Phan (Eds.), Atlas of Hematopathology, 2nd Edition, Academic Press, 2018, pp. 29–56, doi:10.1016/B978-0-12-809843-1.00002-4.
[119] M. Mohty, J. Gautier, F. Malard, M. Aljurf, A. Bazarbachi, C. Chabannon, M.A. Kharfan-Dabaja, B.N. Savani, H. Huang, S. Kenderian, A. Nagler, M.A. Perales, CD19 chimeric antigen receptor-T cells in B-cell leukemia and lymphoma: current status and perspectives, Leukemia 33 (2019) 2767–2778, doi:10.1038/s41375-019-0615-5.
[120] N. Boissel, A. Baruchel, Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children? Blood 132 (2018) 351–361, doi:10.1182/blood-2018-02-778530.
[121] S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, S.A. Grupp, Tisagenlecleucel in children and young adults with b-cell lymphoblastic leukemia, N. Engl. J. Med. 378 (2018) 439–448, doi:10.1056/NEJMoa1709866.
[122] R.H. Scheuermann, E. Racila, CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy, Leuk. Lymphoma 18 (1995) 385–397, doi:10.3109/10428199509059636.
[123] R. Mohanty, C.R. Chowdhury, S. Arega, P. Sen, P. Ganguly, N. Ganguly, CAR T cell therapy: a new era for cancer treatment (Review), Oncol. Rep. 42 (6) (2019) 2183–2195 2019, doi:10.3892/or.2019.7335.
[124] D. Nagorsen, P. Kufer, P.A. Baeuerle, R. Bargou, Blinatumomab: a historical perspective, Pharmacol. Ther. 136 (2012) 334–342, doi:10.1016/j.pharmthera.2012.07.013.
[125] L.M. Hoffman, L. Gore, Blinatumomab, a Bi-specific anti-CD19/CD3 BiTE(®) antibody for the treatment of acute lymphoblastic leukemia: perspectives and current pediatric applications, Front. Oncol. 4 (2014) 63, doi:10.3389/fonc.2014.00063.
[126] N. Gökbuget, H. Dombret, M. Bonifacio, A. Reichle, C. Graux, C. Faul, H. Diedrich, M.S. Topp, M. Brüggemann, H.A. Horst, V. Havelange, J. Stieglmaier, H. Wessels, V. Haddad, J.E. Benjamin, G. Zugmaier, D. Nagorsen, R.C. Bargou, Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia, Blood 131 (2018) 1522–1531 doi.org/, doi:10.1182/blood-2017-08-798322.
[127] S. Paul, C.R. Rausch, P.E. Nasnas, H. Kantarjian, E.J. Jabbour, Treatment of relapsed/refractory acute lymphoblastic leukemia, Clin. Adv. Hematol. Oncol. 17 (2019) 166–175 PMID: 30969955.
[128] M.S. Topp, P. Kufer, N. Gökbuget, M. Goebeler, M. Klinger, S. Neumann, H.A. Horst, T. Raff, A. Viardot, M. Schmid, M. Stelljes, M. Schaich, E. Degenhard, R. Köhne-Volland, M. Brüggemann, O. Ottmann, H. Pfeifer, T. Burmeister, D. Nagorsen, M. Schmidt, R. Lutterbuese, C. Reinhardt, P.A. Baeuerle, M. Kneba, H. Einsele, G. Riethmüller, D. Hoelzer, G. Zugmaier, R.C. Bargou, Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival, J. Clin. Oncol. 29 (2011) 2493–2498, doi:10.1200/JCO.2010.32.7270.
[129] M.S. Topp, N. Gökbuget, G. Zugmaier, E. Degenhard, M.E. Goebeler, M. Klinger, S.A. Neumann, H.A. Horst, T. Raff, A. Viardot, M. Stelljes, M. Schaich, R. Köhne-Volland, M. Brüggemann, O.G. Ottmann, T. Burmeister, P.A. Baeuerle, D. Nagorsen, M. Schmidt, H. Einsele, G. Riethmüller, M. Kneba, D. Hoelzer, P. Kufer, R.C. Bargou, Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL, Blood 120 (2012) 5185–5187, doi:10.1182/blood-2012-07-441030.
[130] D.A. Berry, S. Zhou, H. Higley, L. Mukundan, S. Fu, G.H. Reaman, B.L. Wood, G.J. Kelloff, J.M. Jessup, J.P. Radich, Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis, JAMA Oncol. 3 (2017) e170580, doi:10.1001/jamaoncol.2017.0580.
[131] A. von Stackelberg, F. Locatelli, G. Zugmaier, R. Handgretinger, T.M. Trippett, C. Rizzari, P. Bader, M.M. O'Brien, B. Brethon, D. Bhojwani, P.G. Schlegel, A. Borkhardt, S.R. Rheingold, T.M. Cooper, C.M. Zwaan, P. Barnette, C. Messina, G. Michel, S.G. DuBois, K. Hu, M. Zhu, J.A. Whitlock, L. Gore, Phase I/Phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia, J. Clin. Oncol. 34 (2016) 4381–4389, doi:10.1200/JCO.2016.67.3301.
[132] C.F. Contreras, C.S. Higham, A. Behnert, K. Kim, E. Stieglitz, S.K. Tasian, Clinical utilization of blinatumomab and inotuzumab immunotherapy in children with relapsed or refractory B-acute lymphoblastic leukemia, Pediatr. Blood Cancer 2020 (2020) e28718, doi:10.1002/pbc.28718.
[133] F. Locatelli, G. Zugmaier, N. Mergen, P. Bader, S. Jeha, P.G. Schlegel, J.P. Bourquin, R. Handgretinger, B. Brethon, C. Rossig, C. Chen-Santel, Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia: results of the RIALTO trial, an expanded access study, Blood Cancer J. 10 (2020) 77 Published 2020 Jul 24, doi:10.1038/s41408-020-00342-x.
[134] I. Nagel, M. Bartels, J. Duell, H.H. Oberg, S. Ussat, H. Bruckmueller, O. Ottmann, H. Pfeifer, H. Trautmann, N. Gökbuget, A. Caliebe, D. Kabelitz, M. Kneba, H.A. Horst, D. Hoelzer, M.S. Topp, I. Cascorbi, R. Siebert, M. Brüggemann, Hematopoietic stem cell involvement in BCR-ABL1-positive ALL as a potential mechanism of resistance to blinatumomab therapy, Blood 130 (2017) 2027–2031 doi.org/, doi:10.1182/blood-2017-05-782888.
[135] I. Abou Dalle, E. Jabbour, N.J. Short, F. Ravandi, Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia, Curr. Treat. Opt. Oncol. 20 (2019) 4, doi:10.1007/s11864-019-0603-z.
[136] S. Elitzur, N. Arad-Cohen, S. Barzilai-Birenboim, M. Ben-Harush, B. Bielorai, R. Elhasid, T. Feuerstein, G. Gilad, A. Gural, M. Kharit, N. Litichever, R. Nirel, S. Weinreb, O. Wolach, A. Toren, S. Izraeli, E. Jacoby, Blinatumomab as a bridge to further therapy in cases of overwhelming toxicity in pediatric B-cell precursor acute lym-

phoblastic leukemia: report from the Israeli study group of childhood leukemia, Pediatr. Blood Cancer 66 (10) (2019) e27898, doi:10.1002/pbc.27898.
[137] St. Jude Children's Research Hospital., 2017. Total therapy XVII for newly diagnosed patients with acute lymphoblastic leukemia and lymphoma (ClinicalTrials.gov Identifier: NCT03117751. Retrieved from https://clinicaltrials.gov/ct2/show/study/NCT03117751.
[138] Barz Leahy, Stanley A., Myers K.J., DiNofia R.M., Wray A.M., S.R. Rheingold, C. Callahan, D. Baniewicz, A.E. Barry, M.M. Patino, S.P. Hunger, S. Grupp, D.M. Barrett, S.L. Maude, Cytogenetic characteristics and outcomes of patients receiving CTL019 CAR T cell therapy, Blood 134 (Supplement_1) (2019) 1464, doi:10.1182/blood-2019-130060.
[139] T. Anagnostou, I.B. Riaz, S.K. Hashmi, M.H. Murad, S.S. Kenderian, Anti-CD19 chimeric antigen receptor T-cell therapy in acute lymphocytic leukaemia: a systematic review and meta-analysis, Lancet Haematol. 7 (2020) e816–e826, doi:10.1016/S2352-3026(20)30277-5.
[140] I. Aldoss, A.S. Stein, Advances in adult acute lymphoblastic leukemia therapy, Leuk. Lymphoma 59 (2018) 1033–1050, doi:10.1080/10428194.2017.1354372.
[141] D.J. DeAngelo, A.S. Advani, D.I. Marks, M. Stelljes, M. Liedtke, W. Stock, N. Gökbuget, E. Jabbour, A. Merchant, T. Wang, E. Vandendries, A. Neuhof, H. Kantarjian, S. O'Brien, Inotuzumab ozogamicin for relapsed/refractory acute lymphoblastic leukemia: outcomes by disease burden, Blood Cancer J. 10 (2020) 81 Published 2020 Aug 7, doi:10.1038/s41408-020-00345-8.
[142] D. Bhojwani, R. Sposto, N.N. Shah, V. Rodriguez, C. Yuan, M. Stetler-Stevenson, M.M. O'Brien, J.L. McNeer, A. Quereshi, A. Cabannes, P. Schlegel, C. Rossig, L. Dalla-Pozza, K. August, S. Alexander, J.P. Bourquin, M. Zwaan, E.A. Raetz, M.L. Loh, S.R. Rheingold, Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia, Leukemia 33 (2019) 884–892, doi:10.1038/s41375-018-0265-z.
[143] M.M. O'Brien, L. Ji, N.N. Shah, S.R. Rheingold, D. Bhojwani, J.S. Yi, C.M. Yuan, A.C. Harris, P.A. Brown, M.J. Borowitz, O. Militano, M. Devidas, E.A. Raetz, L. Gore, M.L. Loh, A phase 2 trial of inotuzumab ozogamicin (InO) in children and young adults with relapsed or refractory (R/R) CD22+ B-acute lymphoblastic leukemia (B-ALL): results from children's oncology group protocol AALL1621, Blood 134 (Supplement_1) (2019) 741, doi:10.1182/blood-2019-128977.
[144] E. Brivio, F. Locatelli, M. Lopez-Yurda, A. Malone, C. Diaz de Heredia, B. Bielorai, C. Rossig, V.H.J. van der Velden, A.C.J. Ammerlaan, A. Thano, I.M. van der Sluis, M.L. Den Boer, Y. Chen, B. Sleight, B. Brethon, K. Nysom, L. Sramkova, I. Øra, L. Vinti, C. Chen-Santel, C.M. Zwaan, A Phase I study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study), Blood (2020) blood.2020007848, doi:10.1182/blood.2020007848.
[145] P. Dwivedi, D.E. Muench, M. Wagner, M. Azam, H.L. Grimes, K.D. Greis, Time resolved quantitative phospho-tyrosine analysis reveals Bruton's Tyrosine kinase mediated signaling downstream of the mutated granulocyte-colony stimulating factor receptors, Leukemia 33 (2019) 75–87, doi:10.1038/s41375-018-0188-8.
[146] H.R. Robinson, J. Qi, E.M. Cook, C. Nichols, E.L. Dadashian, C. Underbayev, S. Herman, N.S. Saba, K. Keyvanfar, C. Sun, I.E. Ahn, S. Baskar, C. Rader, A. Wiestner, A CD19/CD3 bispecific antibody for effective immunotherapy of chronic lymphocytic leukemia in the ibrutinib era, Blood 132 (2018) 521–532, doi:10.1182/blood-2018-02-830992.
[147] F. Zi, L. Yu, Q. Shi, A. Tang, J. Cheng, Ibrutinib in CLL/SLL: from bench to bedside (Review), Oncol. Rep. 42 (2019) 2213–2227, doi:10.3892/or.2019.7364.
[148] E. Kim, C. Hurtz, S. Koehrer, Z. Wang, S. Balasubramanian, B.Y. Chang, M. Müschen, R.E. Davis, J.A. Burger, Ibrutinib inhibits pre-BCR+ B-cell acute lymphoblastic leukemia progression by targeting BTK and BLK, Blood 129 (2017) 1155–1165, doi:10.1182/blood-2016-06-722900.
[149] P.A. Goodman, C.M. Wood, A.O. Vassilev, C. Mao, F.M. Uckun, Defective expression of Bruton's tyrosine kinase in acute lymphoblastic leukemia, Leuk. Lymphoma 44 (2003) 1011–1018, doi:10.1080/1042819031000067576.
[150] L.F. Boullosa, P. Savaliya, S. Bonney, L. Orchard, H. Wickenden, C. Lee, E. Smits, A.H. Banham, K.I. Mills, K. Orchard, B.A. Guinn, Identification of survivin as a promising target for the immunotherapy of adult B-cell acute lymphoblastic leukemia, Oncotarget 9 (2017) 3853–3866 Published 2017 Dec 17, doi:10.18632/oncotarget.23380.
[151] S. Jordaens, L. Cooksey, L. Freire Boullosa, V. Van Tendeloo, E. Smits, K.I. Mills, K.H. Orchard, B.A. Guinn, New targets for therapy: antigen identification in adults with B-cell acute lymphoblastic leukaemia, Cancer Immunol. Immunother. 69 (2020) 867–877, doi:10.1007/s00262-020-02484-0.
[152] H. Garg, P. Suri, J.C. Gupta, G.P. Talwar, S. Dubey, Survivin: a unique target for tumor therapy, Cancer Cell. Int. 16 (2016) 49 Published 2016 Jun 23., doi:10.1186/s12935-016-0326-1.
[153] R.A. Fenstermaker, S.A. Figel, J. Qiu, T.A. Barone, S.S. Dharma, E.K. Winograd, P.M. Galbo, L.M. Wiltsie, M.J. Ciesielski, Survivin monoclonal antibodies detect survivin cell surface expression and inhibit tumor growth in vivo, Clin. Cancer Res. 24 (2018) 2642–2652, doi:10.1158/1078-0432.CCR-17-2778.
[154] F. Li, I. Aljahdali, X. Ling, Cancer therapeutics using survivin BIRC5 as a target: what can we do after over two decades of study? J. Exp. Clin. Cancer Res. 38 (2019) 368 Published 2019 Aug 22, doi:10.1186/s13046-019-1362-1.
[155] A.W. Roberts, D. Huang, Targeting BCL2 with BH3 mimetics: basic science and clinical application of venetoclax in chronic lymphocytic leukemia and related B cell malignancies, Clin. Pharmacol. Ther. 101 (2017) 89–98, doi:10.1002/cpt.553.
[156] C.G. Mullighan, S. Jeha, D. Pei, D. Payne-Turner, E. Coustan-Smith, K.G. Roberts, E. Waanders, J.K. Choi, X. Ma, S.C. Raimondi, Y. Fan, W. Yang, G. Song, J.J. Yang, H. Inaba, J.R. Downing, W.H. Leung, W.P. Bowman, M.V. Relling, W.E. Evans, T. Zhang, D. Campana, C.H. Pui, Outcome of children with hypodiploid ALL treated with risk-directed therapy based on MRD levels, Blood 126 (2015) 2896–2899, doi:10.1182/blood-2015-09-671131.
[157] S. Safavi, K. Paulsson, Near-haploid and low-hypodiploid acute lymphoblastic leukemia: two distinct subtypes with consistently poor prognosis, Blood 129 (2017) 420–423, doi:10.1182/blood-2016-10-743765.
[158] C.H. Pui, P. Rebora, M. Schrappe, A. Attarbaschi, A. Baruchel, G. Basso, H. Cavé, S. Elitzur, K. Koh, H.C. Liu, K. Paulsson, R. Pieters, L.B. Silverman, J. Stary, A. Vora, A. Yeoh, C.J. Harrison, M.G. Valsecchi, Outcome of children with hypodiploid acute lymphoblastic leukemia: a retrospective multinational study, J. Clin. Oncol. 37 (2019) 770–779, doi:10.1200/JCO.18.00822.
[159] G. Richard-Carpentier, E. Jabbour, N.J. Short, C.R. Rausch, J.M. Savoy, P. Bose, M. Yilmaz, N. Jain, G. Borthakur, M. Ohanian, Y. Alvarado, M. Rytting, P. Kebriaei, M. Konopleva, H. Kantarjian, F. Ravandi, Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia, Clin. Lymphoma Myeloma Leuk. 20 (2020) 212–218, doi:10.1016/j.clml.2019.09.608.
[160] E. Diaz-Flores, E.Q. Comeaux, K.L. Kim, E. Melnik, K. Beckman, K.L. Davis, K. Wu, J. Akutagawa, O. Bridges, R. Marino, M. Wohlfeil, B.S. Braun, C.G. Mullighan, M.L. Loh, Bcl-2 is a therapeutic target for hypodiploid b-lineage acute lymphoblastic leukemia, Cancer Res. 79 (2019) 2339–2351, doi:10.1158/0008-5472.CAN-18-0236.
[161] N.J. Lacayo, V.A. Pullarkat, W. Stock, E. Jabbour, A. Bajel, J. Rubnitz, J. Leonard, C.G. Mullighan, S.L. Khaw, S.I. Vear, J.T. Opferman, A.H. Salem, M. Schmidt, B. Tong, L. Zhou, J.A. Ross, L. Bensman, A. Jacobson, R. Norris, T. Alexander, Safety and efficacy of venetoclax in combination with navitoclax in adult and pediatric relapsed/refractory acute lymphoblastic leukemia and lymphoblastic lymphoma, Blood 134 (Supplement_1) (2019) 285, doi:10.1182/blood-2019-126977.
[162] S. Farber, L.K. Diamond, Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid, N. Engl. J. Med. 238 (1948) 787–793, doi:10.1056/NEJM194806032382301.
[163] O.H. Pearson, L.P. Eliel, Use of pituitary adrenocorticotropic hormone (ACTH) and cortisone in lymphomas and leukemias, J. Am. Med. Assoc. 144 (1950) 1349–1353, doi:10.1001/jama.1950.02920160023005.
[164] J.H. Burchenal, M.L. Murphy, R.R. Ellison, M.P. Sykes, T.C. Tan, L.A. Leone, D.A. Karnofsky, L.F. Craver, H.W. Dargeon, C.P. Rhoads, Clinical evaluation of a new antimetabolite, 6-mercaptopurine, in the treatment of leukemia and allied diseases, Blood 8 (1953) 965–999 PMID:13105700 .
[165] A.E. Evans, S. Farber, S. Brunet, P.J. Mariano, Vincristine in the treatment of acute leukemia in children, Cancer 16 (1963) 1302–1306 10.1002/1097-0142(196310)16:10<1302::aid−cncr2820161011>3.0.co;2-a.
[166] E. Frei 3rd, M. Karon, R.H. Levin, E.J. Freireich, R.J. Taylor, J. Hananian, O. Selawry, J.F. Holland, B. Hoogstraten, I.J. Wolman, E. Abir, A. Sawitsky, S. Lee, S.D. Mills, E.O. Burgert Jr, C.L. Spurr, R.B. Patterson, F.G. Ebaugh, G.W. James 3rd, J.H. Moon, The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia, Blood 26 (1965) 642–656 PMID:5321112 .
[167] S.E. Karol, C.H. Pui, Personalized therapy in pediatric high-risk B-cell acute lymphoblastic leukemia, Ther. Adv. Hematol. 11 (2020) 2040620720927575 Published 2020 Jun 2, doi:10.1177/2040620720927575.
[168] J.L. Jameson, D.L. Longo, Precision medicine–personalized, problematic, and promising, N. Engl. J. Med. 372 (2015) 2229–2234, doi:10.1056/NEJMsb1503104.
[169] M. Di Sanzo, L. Cipolloni, M. Borro, R. La Russa, A. Santurro, M. Scopetti, M. Simmaco, P. Frati, Clinical applications of personalized medicine: a new paradigm and challenge, Curr. Pharm. Biotechnol. 18 (2017) 194–203, doi:10.2174/1389201018666170224105600.
[170] M. Baccarani, M.W. Deininger, G. Rosti, A. Hochhaus, S. Soverini, J.F. Apperley, F. Cervantes, R.E. Clark, J.E. Cortes, F. Guilhot, H. Hjorth-Hansen, T.P. Hughes, H.M. Kantarjian, D.W. Kim, R.A. Larson, J.H. Lipton, F.X. Mahon, G. Martinelli, J. Mayer, M.C. Müller, D. Niederwieser, F. Pane, J.P. Radich, P. Rousselot, G. Saglio, S. Saußele, C. Schiffer, R. Silver, B. Simonsson, J.L. Steegmann, J.M. Goldman, R. Hehlmann, European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013, Blood 122 (2013) 872–884, doi:10.1182/blood-2013-05-501569.
[171] M.V. Relling, M. Schwab, M. Whirl-Carrillo, G. Suarez-Kurtz, C.H. Pui, C.M. Stein, A.M. Moyer, W.E. Evans, T.E. Klein, F.G. Antillon-Klussmann, K.E. Caudle, M. Kato, A. Yeoh, K. Schmiegelow, J.J. Yang, Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update, Clin. Pharmacol. Ther. 105 (2019) 1095–1105, doi:10.1002/cpt.1304.
[172] FDA-Approved Drugs. United States food and drug administration (FDA). https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed November 11, 2020).