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Pharmacogenetics predictive of response and toxicity in acute lymphoblastic leukemia therapy

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Abstract

Acute lymphoblastic leukemia (ALL) is a relatively rare disease in adults accounting for no more than 20% of all cases of acute leukemia. By contrast with the pediatric population, in whom significant improvements in long term survival and even cure have been achieved over the last 30 years, adult ALL remains a significant challenge. Overall survival in this group remains a relatively poor 20–40%. Modern research has focused on improved pharmacokinetics, novel pharmacogenetics and personalized principles to optimize the efficacy of the treatment while reducing toxicity. Here we review the pharmacogenetics of medications used in the management of patients with ALL, including L-asparaginase, glucocorticoids, 6-mercaptopruine, methotrexate, vincristine and tyrosine kinase inhibitors. Incorporating recent pharmacogenetic data, mainly from pediatric ALL, will provide novel perspective of predicting response and toxicity in both pediatric and adult ALL therapy.

Keywords

Acute lymphoblastic leukemia; Pharmacogenetics; L-asparaginase; Glucocorticoids; 6-Mercaptopruine; Methotrexate; Vincristine; Tyrosine kinase inhibitors

Introduction

Acute lymphoblastic leukemia (ALL) is a malignancy of immature lymphoid progenitors which has historically been classified into precursor T cell leukemia, precursor B cell leukemia and mature (Burkitt) leukemia [1, 2]. According to National Cancer Institute

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Conflict of interest

Dr. Meir Wetzler is a consultant for Sigma Tau, Jazz Pharmaceuticals and Novartis.

Dr. Elizabeth Griffiths is a consultant for Alexion Pharmaceuticals, Norvartis and Celgene and receives grant funding from Astex Pharmaceuticals.

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Surveillance, Epidemiology, and End Results Program, 6,070 new cases were diagnosed in the United States in 2013. Childhood ALL accounts for the majority of these cases, responsible for almost a third of all childhood cancer in children aged from 0 to 14 years [3]. In the past 20 years, the 5-year survival rate of childhood ALL has increased from less than 40% in the mid-1960s to 91% in the mid-2000s [3]. This result was achieved by optimal use of existing anti-leukemic drugs, combinations with newly developed tyrosine kinase inhibitors and improvements in supportive care. Unfortunately, the long-term survival rate for older patients remains poor. Long term remission are achieved in 50%–60% of patients between aged 15–45, about 30% of patients aged 45–54 and in older adults the five year survival is rarely better than 15% in older adults [4–6].

The typical treatment course for patients diagnosed with precursor-type ALL lasts 2–3 years, and includes remission-induction therapy, consolidation therapy and maintenance. Induction generally includes glucocorticoids, vincristine, and L-asparaginase, with or without an anthracycline [7]. Consolidation therapy is given after induction therapy to eradicate minimal residual leukemia cells. High dose methotrexate (MTX) with 6-mercaptopurine (6-MP) are commonly used, accompanied by frequent pulses of vincristine, glucocorticoids and L-asparaginase for 20–30 weeks. Maintenance therapy generally lasts for 2 years and is comprised of 6-MP and weekly MTX with or without pulsed doses of vincristine and dexamethasone [7]. The frequent and multiple therapies required for the treatment of ALL result in significant toxicity which can contribute both to early morbidity and mortality as well as significant long term sequelae [8]. Many factors have the potential to contribute to the occurrence of serious side effects. Specific genetic polymorphisms have recently been identified as crucial variables in the toxicity and efficacy of drug therapy for management of ALL.

A large scale genome-wide analysis including 2,534 children with ALL found that genomic variation in Native American ancestry was independently associated with higher risk of relapse, suggesting a crucial role for pharmacogenetic effects in ALL [9]. In this review, we will summarize recent progress in pharmacogenetic research and how these achievements will potentially contribute to patient specific tailoring of ALL treatment regimens (Table 1.).

L-Asparaginase

L-asparaginase is a common component in the initial treatment of ALL, particularly in intensive induction therapy. Three asparaginase preparations were available: one derived from *Escherichia coli* (*E.Coli* asparaginase, recently removed from the market), the former's pegylated form (PEG-asparaginase) and the third is a product isolated from *Erwinia caratovora* (*Erwinia* asparaginase) [10–12]. Treatment with asparaginase has been associated with serious adverse effects, including allergy, pancreatitis and cerebrovascular accidents. Hypersensitivity responses, more commonly observed with native *E.coli* asparaginase [13], occur in up to 35% of patients and 10% of those reactions are life-threatening anaphylaxis [10, 14]. PEG-asparaginase demonstrates a prolonged half-life and decreased renal excretion relative to the parent compound [15]. In addition, the pegylated formulation increases efficacy and reduces the possibility of antibody generation by preventing reticuloendothelial uptake [16, 17]. The newly developed *Erwinia* asparaginase

produced a lower rate of allergic reaction and has been demonstrated to produce effective asparaginase activity even in patients who had previously experienced an allergy to PEG-asparaginase [18]. Four different pharmacogenetic targets have been identified to have a relationship to asparaginase toxicity.

Asparagines synthetase (ASNS) catalyzes the transfer of an amino group to aspartic acid to form asparagines. Leukemic blasts are devoid of ASNS, explaining the utility of the different L-asparaginases. Early research has unraveled that ASNS activity was an indicator of L-asparaginase resistance *in vitro* [19, 20] and in clinical studies. The single-nucleotide polymorphisms (SNPs) of the basic leucine zipper activating transcription factor 5 (*ATF5*), inducing increased ASNS activity, were associated with reduced event-free survival (EFS) [21]. Similarly, Pastorczak *et al.* recently reported that polymorphism of a 14-bp tandem repeat sequence in the *ASNS* gene itself leads to higher expression of the gene, which was associated with worse response and increased risk for relapse [22]. These retrospective and single-center studies have provided intriguing evidence for a significant pharmacogenomics contribution to therapeutic efficacy, although some of these results remain controversial and require confirmation through prospective clinical trials.

Chen *et al.* studied more than 500,000 SNPs in 485 children with ALL. Five SNPs with an identical relationship to different alleles of the glutamate α-amino-3-hydroxy-5-methyl-4-isocazolepropionic acid (AMPA) receptor subunit 1 gene (*GRIA1*) were associated with hypersensitivity to asparaginase [23]. *GRIA1* gene encodes a subunit of glutamate receptor 1, which is a predominant excitatory neurotransmitter receptor in the brain. In addition, glutamate has recently been recognized as an immune modulator [24].

Furthermore, recent report demonstrated an association between HLA-DRB1*0701 with asparaginase allergy due to amino acid variants within the binding pocket of HLA-DRB1 that conferred higher binding affinity [25]. Highlighting the potential importance of such genetic variability to predict adverse drug effect the Food and Drug Administration (FDA) recently approved testing for HLA-B*5701 prior to the administration of abacavir, to patients with human immunodeficiency virus (HIV) as a mean of avoiding drug toxicity [26, 27]. Identification of genetic polymorphisms which predict drug toxicity provides a new paradigm for the incorporation of pharmacogenetics into routine clinical practice, although additional prospective evidence proving these associations may be required.

Glucocorticoids

Glucocorticoids are the keystone of ALL therapy. They exert their activity by reducing cell proliferation and promoting apoptosis or cell arrest by binding to intracytoplasmic glucocorticoid receptors. In tumor cells, up-regulation of P-glycoprotein, encoded by the ATP-binding cassette sub-family B1 (*ABCB1*) gene, is responsible for glucocorticoid resistance. *C3435T* [28], *G2677T/A* [29] and *T129C* [30] have been identified as polymorphisms associated with possible glucocorticoid resistance based on *in vitro* studies. Better responses to glucocorticoids therapies have been observed in patients with the *A1082G* SNP in the promoter region of the *interleukin-10* (IL-10) gene [31]. The SNP results in up-regulated IL-10 expression and increases the binding of glucocorticoids to

monocytes. Likewise, deletion of the *glutathione-S-transferase* (*GSTs*) *type M1* gene has been associated with initial responsiveness to glucocorticoids as well as the severity of infectious complication by decreasing glucocorticoid metabolism [32, 33]. In B-cell ALL, Pottier *et al.* showed that mutations in three subunits of the nucleosome-remodeling complex correlate with *in vitro* glucocorticoid resistance using a panel of 177 primary pediatric ALL samples [34]. Further, Real *et al.* demonstrated that the NOTCH pathway is a pivotal determinant of glucocorticoid sensitivity in T-cell ALL. Combination therapy with a gamma-secretase inhibitor (inhibitor of NOTCH1) and glucocorticoids could restore the anti-leukemic effect of glucocorticoids in glucocorticoid-resistant T-cell ALL [35]. In addition, gene expression profiles of carbohydrate metabolism have revealed that increased glucose metabolism can induce prednisolone resistance [36]. Inhibition of molecules in the glycolytic pathway, for example glyceraldehydes-3-phosphate dehydrogenase (GAPDH) and 2-deoxy-D-glucose (2-DG), reverse glucocorticoid resistance in both cell lines and primary ALL samples [36]. Similarly, overexpression of the X-linked inhibition of apoptosis protein (XIAP) has been shown to predict chemotherapy resistance. In childhood with T-cell ALL, poor prednisone response was associated with increased XIAP expression, and glucocorticoid resistance could be reversed by XIAP inhibition [37]. Recent reports from Jones *et al.* have shown that reduced expression of Transducin Beta-Like 1 X-linked Receptor 1 (TBL1XR1) induces glucocorticoid resistance in a B-cell ALL cell line by decreasing glucocorticoid receptor affinity [38]. More recently, gene expression microarray studies performed on samples from 256 primary pediatric B-cell ALL patients have identified overexpression of epithelial membrane protein 1 (*EMP1*) as a novel poor prognostic factor and possible drug target important for the regulation of *in vitro* prednisolone resistance [39].

Glucocorticoids have a number of long-term adverse effects, including hypertension, diabetes, infection, osteoporosis and avascular necrosis (AVN). Kamden *et al.* determined the genotypes for 203 candidate SNPs in pediatric ALL, which were previously linked to hypertension or metabolism of anti-leukemic agents. This study identified eight genes associated with steroid-induced hypertension [40]. Furthermore, Jones *et al.* have shown that corticotrophin-releasing hormone receptor 1 (*CRHR1*) polymorphisms may impact the risk of bone mineral density loss in a study of 309 long-term ALL survivors [41]. A total of 10–15% of children develop AVN after receiving ALL treatment, and this complication can be directly attributable to the prolonged use of high-dose glucocorticoids [42, 43]. A previous case report suggested variants of thymidylate synthase (TYMS) were associated with a higher risk for developing AVN [44]; however, these results were not confirmed in subsequent studies [45]. Instead, prospective evaluation identified a SNP of plasminogen activator inhibitor-1 (*PAI-1*) as a candidate for the prediction of osteonecrosis [45]. Genome-wide association studies unraveled polymorphisms of acid phosphatase 1 (*ACP1*), which regulates lipid levels and osteoblast differentiation, as a potential predictor of osteonecrosis risk [46]. Three genes (*alpha-2-HS-glycoprotein*, *IL-6*, *polymerase delta interacting protein 3*) were significantly associated with dexamethasone-induced sleep disturbance [47]. In summary, it is clear that the adverse effects of glucocorticoids are linked to differential rates of clearance mediated by population variant as well as interaction with

other cytokines. Prospective validation for the predictive value of such SNPs may in the future allow better prediction of severe side effects from glucocorticoids.

6-Mercaptopurine (6-MP)

6-MP is an antimetabolite used for more than 40 years. Combined with weekly MTX, daily 6-MP is the backbone of maintenance therapy for ALL, with or without pulses of vincristine and dexamethasone. After being metabolized to 6-thioguanine nucleotides (6-TG), it inhibits *de-novo* purine synthesis. Bhatia *et al.* reported that absolute 6-MP or 6-TG levels were not helpful for prognosticating relapse risk in a study including 744 pediatric patients who had achieved remission. Instead, high intra-individual variability in 6-TG levels contributed to relapse risk in this population, which reinforce the need to minimize the fluctuation of 6-MP [48].

The enzyme, thiopurine methyltransferase (TPMT) catalyzes the S-methylation of thiopurine to an inactive metabolite. These genes are co-dominantly inherited, containing nonsynonymous SNPs, leading to significant differences in enzyme activity and important clinical consequences [49]. Patients with *TPMT* SNPs associated with lower enzymatic activity, either heterozygous or homozygous can cause moderate to severe myelosuppression when treated with conventional doses of 6-MP [50]. Similarly, homozygosity for the *TPMT* deficient SNP can result in greater risk for radiation-induced brain tumors and chemotherapy-induced acute myeloid leukemia [51], although these patients tend to have a lower rate of relapse rate [52]. Since 3–14% of patients are heterozygous for *TPMT* associated with lower enzyme activity, routine pre-treatment testing is suggested and once identified, these patients should start with a dose reduction in the 6-MP level by 30–70% [53]. Notably, the FDA now recommends testing for the most commonly identified inactive SNP genotype, which can prospectively predict patients at higher risk of developing 6-MP-induced hematopoietic toxicity [16, 49, 50]. It is most useful in ALL protocols containing high doses 6-MP (>50 mg/m^2/day) [5]. At St Jude Children's Research Hospital, *TPMT* gene is evaluated in all patients at the diagnosis of ALL. It has been shown that in the ALL protocol using 6-MP at 75 mg/m^2/day, prospective adjustment of 6-MP based on *TPMT* status allowed successful treatment at reduced dose with comparable toxicity and efficacy to those patients with wild-type *TPMT* [49, 54, 55].

In addition to TPMT, inosine triphosphate pyrophosphatase (ITPA) is another candidate enzyme involved in 6-MP metabolism. ITPA catalyzes the hydrolysis of inosine triphosphate (ITP) to inosine monophasphate (IMP) [53]. Studies performed by Stocco *et al.* demonstrated that non-functional ITPA was associated with higher concentrations of methylated nucleotide metabolites of 6-MP in patients' leukemia cells adjusted for *TPMT* genotype [55, 56]. A recent report replicated this observation, showing that methylated 6-MP concentrations are higher in wild-type *TPMT*/variant *ITPA* patients [57]. Two SNPs associated with defective *ITPA* gene function, *rs1127354* (Pro32Thr) and *IVS2+21A>C*, were identified in approximately 10% of Caucasians, leading to a higher risk for 6-MP induced toxicity [58, 59]. Therefore, identification of variant *ITPA* SNPs may be the next pharmacogenomics test adopted into clinical practice.

Methotrexate (MTX)

MTX is a folate inhibitor introduced into clinical practice in the 1950s and remains a major component of approach to ALL therapy. MTX suppresses DNA synthesis by competitively inhibiting the enzyme dihydrofolate reductase (DHFR) thus interrupting thymidine biosynthesis. Multiple transporters and enzymes participate in the metabolism of folate, and many of these demonstrate genetic polymorphisms which may impact the metabolism and activity of MTX [60].

MTX enters cells via a transporter, called reduced folate carrier 1 (RFC-1) or solute carrier family 19 member 1 (SLC19A1) [61]. Impaired function of this transporter has been recognized as a major mechanisms for MTX resistance [62]. A common variant of *RFC-1*, *G80A* is associated with decreased inward MTX transportation [63]. Furthermore, Laverdiere *et al.* demonstrated that pediatric ALL patients with the *G80A* variant of *RFC-1* had worse prognosis manifested by increased relapse rate and decreased EFS, than those carrying the GG genotype [64]. In contrast with these results, other studies failed to reveal a relationship between disease outcome and *RFC-1* polymorphisms. These data may be explained by differences in the doses of MTX used in the two studies. At higher dose (5 g/m^2 body surface area), MTX can enter cells via passive diffusion, and thus polymorphisms resulting in decreased transporter mediated influx may be less significant [65, 66].

Solute carrier organic anion transporter 1B1 (SLCO1B1) is another MTX carrier mainly located on human hepatocytes. Two SNPs in *SLCO1B1*, *rs11045879* and *rs4149081* have been linked to MTX clearance across regimens and with severe gastrointestinal toxicity during consolidation therapy [67]. Subsequent studies from other research groups have validated these SNPs as contributing to clinical outcome [68, 69]. A recent report from Radtke *et al.* demonstrated that the *SLCO1B1 rs4149056* variant was significantly associated with MTX kinetics. MTX area under the concentration time curve $(AUC)_{0–48h}$ increased by 26% in the presence of *rs4149056* [65]. From deep re-sequencing of *SLCO1B1* exons in 699 children, four common *SLCO1B1* haplotypes were associated with the lowest MTX clearance. Differences in this gene can account for 10.7% of the population variability in MTX clearance [70]. Therefore, *SLCO1B1* SNPs are significant determinants for MTX toxicity, especially stomatitis and mucositis during consolidation therapy.

Methylenetetrahydrofolate reductase (*MTHFR*) is the most extensively studied gene in MTX metabolism. It catalyzes the conversion of 5,10-methylene-tetrahydrofolate to 5-methyl-tetrahydrofolate, which serves as a methyl donor to convert homocysteine to methionine [71]. Two SNPs, *C677T* (*rs1901133*) resulting in substitution of alanine with valine at codon 222 (Ala222Val) [72] and *A1298C* (*rs1801131*) resulting in substitution of alanine for glutamic acid at codon 429 (Glu429Ala) [73] have been related to reduced activity of MTHFR and increased MTX level. Some case reports demonstrated that the *C677T* (*rs1901133*) variant induced neurotoxicity [74] and liver toxicity [75], whereas, other publications failed to confirm this relationship [76, 77]. A study that recruited 520 children with ALL demonstrated that the *C677T* variant allele was significantly associated with relapse without increased risk of toxicity or infection [77]. In the ALL- Berlin-Münster-Frankfurt (BFM) 2000 study population, *MTHFR A1298C* (*rs1801131*) was associated with

minimal residual disease and shorter EFS, with a hazard ratio of 7.3 [65]. However, Chiusolo *et al.* reported that the *C677T* (*rs1901133*) and *A1298C* (*rs1801131*) alleles were not significant in predictors of relapse free survival or EFS in Thai pediatric ALL patients (n=76), but were associated with increased susceptibility to hematopoietic and hepatotoxicity doses ranging from 15–30 mg/m^2 [78]. These different results make it difficult to draw any strong conclusions about the role of *MTHFR* SNPs in predicting MTX toxicity and response. Variability may stem from differences in the treatment protocols across the different studies with inconsistent doses of MTX, small number of patients and other confounding factors, like other SNPs or ethnic heterogeneity between Asian and Northern European patient populations.

Blood MTX levels have not been demonstrated to reliably predict disease outcome [64]. Accumulation of the active metabolites of MTX, however, such as MTX polyglutamates (MTXPGs), have been associated with anti-leukemic activity [7, 11, 71]. MTX and MTXPG inhibit TYMS and subsequently suppress DNA synthesis. Double or triple tandem repeats of *TYMS* gene participate in enhancing TYMS expression and activity and thus have been postulated to result in MTX resistance. Krajinovic *et al.* studied 205 children with ALL who were treated with MTX and showed that individuals who were homozygous for triple repeats (3R) had worse outcome when compared with children with other genotypes [79]. A subsequent study extended to 259 children with ALL confirmed the finding that 3R increased the risk of relapse and fatal outcome [80]. By contrast, results from Lauten *et al.* did not demonstrate a relationship between *TYMS* 3R polymorphism and ALL relapse, making this association ambiguous [81]. To date, the association between the *TYMS* gene polymorphisms and ALL outcomes remains uncertain.

Although most of the studies in the literature have focused exclusively on coding genes, corresponding to only 1.5% of the entire genome, emerging data has supported the importance of microRNAs (miRNAs), small non-coding RNAs that regulate gene expression in a post-transcriptional manner in ALL. miRNAs can regulate genes involved in drug transportation, metabolism and targeting. Consequently, studies of variant miRNAs in patients may shed further light on new aspects of drug-resistance. For example, SNP *829C>T*, near the miR-24 binding site of *DHFR*, causes elevation of DHFR expression [82]. The ATP-binding cassette sub-family C (ABCC), which are efflux MTX transporters, is down-regulated by miRNA SNPs, leading to increased MTX levels. Similarly, up-regulation of miR-453 decreases the activity of *ABCC1*, *ABCB1*, *ABCC2* and *ABCC4* genes, leading to increased MTX levels and toxicity [83]. Presence of the SNP of *rs639174* in *DROSHA* gene, which encodes the enzyme RNAse III processing miRNA, was related to gastrointestinal toxicity induced by MTX in pediatric B-cell ALL patients. This study was the first to demonstrate a potential role for polymorphisms in miRNA processing genes to predict for toxicity in ALL management [84]. Further studies of miRNA, epigenetics and genome-wide screening will better elucidate the individual variability in MTX efficacy and toxicity.

Vincristine

Vincristine binds to tubulin dimers, interfering with microtubule formation and thereby mitotic spindle dynamics, and resulting in mitotic arrest and leukemic cell death in

metaphase. Vincristine-induced neurotoxicity, characterized by constipation and motorsensory dysfunction remains a serious and largely unpredictable problem for patients with ALL. The cytochrome P450 enzyme (CYP) 3A5 is responsible for 55–59% of total vincristine metabolism [85]. An early study revealing variable grades of neurotoxicity between Caucasians (34.8%) and African-Americans (4.8%) suggested a role for polymorphisms in CYP3A5 in vincristine-induced toxicities [86]. Another study involving 616 pediatric ALL patients did not find an association between EFS and CYP3A5 polymorphisms in ALL patients [87]. However, a sub-group evaluation from this study demonstrated that in T-cell ALL patients the *CYP3A5*36986A>G* allele, which leads to low expression of CYP3A5, had an eight times higher relapse rate, indicating a specific role for CYP3A5 in T-cell ALL [87]. In pre-B ALL, expression of *CYP3A5* was associated with less vincristine-induced peripheral neuropathy compared to non-expressors [88]. This effect may be achieved by a lower ratio of vincristine to its' primary metabolite (M1) [88]. Despite these intriguing results, two other studies, which enrolled a total of 86 patients, and evaluated the presence of *CYP3A5*3*, *CYP3A5*6* and *ABCB1* SNPs failed to confirm a significant association with the occurrence of vincristine-induced side effects [89–91]. These studies are limited due to the small number of patients included. In a recent abstract, investigators performed genome-wide SNP analysis in 321 pediatric ALL patients and demonstrated that variants of *rs924607* localized to chromosome 5 within the promoter region of centrosomal protein of 72 kDa (*CEP72*), were linked to altered risks of vincristine-induced neuropathy [92]. Larger scale prospective studies, including a wider range of genotypic variants, are needed to address which SNPs best predict vincristine-induced neurotoxicity in ALL patients.

Tyrosine kinase inhibitor (TKI)

The Philadelphia chromosome (Ph) is the most common cytogenetic aberration in adult ALL. Translocation of genetic material between chromosomes 9 and 22 [t(9,22)(q34;q11)] produces a fusion gene *BCR-ABL1*, which result in a constitutively active tyrosine kinase [4]. Only 5% of children and those younger than 20 demonstrate Ph-chromosome positive ALL; but, the incidence increases to 33% in patients 20–40 years, 49% in those over 40 years and decreases to 35% in those over 60 years [4, 93, 94]. Combining the BCR-ABL1 inhibitor, imatinib, with conventional chemotherapy has increased the complete remission (CR) rate in these patients to 95%, and improved 3-year overall survival (OS) rate to >50%. Fielding *et al.* demonstrated that the inclusion of imatinib resulted in a significant improvement in long-term outcomes using a large database of clinical trials for Ph-positive ALL conducted prior to and after the development of imatinib therapy in the United Kingdom [95]. The 4-year OS was 38% in the imatinib cohort as compared with 22% in the chemotherapy only cohort [95]. Despite these results, Ph+ ALL patients exhibit heterogeneous responses to TKIs. This has been attributed to the presence of additional genetic abnormalities, for example, the Ikaros family zinic finger protein 1 (*IKZF1*) gene deletion [96], novel *BCR-ABL1* gene mutations, or disruption of drug transportation [4].

Patients have also demonstrated wide inter-individual variability in the metabolism of imatinib which is mediated by CYP3A4/5 [97]. Although a number of polymorphisms in genes affecting drug transport and DNA repair have been associated with drug efficacy [98,

99], pharmacogenetic studies of toxicity are rare. While patients with the TT genotype of *ABCB1* gene loci 1236, 2677 and 3435 demonstrated higher drug clearance rate, individuals without these SNPs also did not demonstrate any significant toxicity related to higher drug levels [100]. Several reports have shown that *CYP2D6*4* [101] or *ABCG2421A* variant alleles [102] may contribute to increased adverse effects. However, these data are not convincing enough to be conclusive, and most of the studies were performed in patients with chronic myeloid leukemia (CML) or gastrointestinal stromal tumors, not Ph+ ALL. It is important to note that, in contrast to CML, responses to imatinib in patients with Ph+ ALL are generally short-lived with high rates of relapse. When they do so, many of leukemia cells demonstrate novel point mutations in the *BCR-ABL1* kinase or adjacent domain rendering them resistance to imatinib therapy [4, 103]. Although second-generation *BCR-ABL1* TKIs, such as dasatinib and nilotinib, appear to be safe and efficacious in imatinib resistant ALL patients, the emergence of T315I and other resistance conferring *BCR-ABL1* mutations, lead to treatment failure [104]. More research is needed in order to better personalize TKI management in the treatment of Ph+ ALL.

Perspectives

Substantial changes have occurred in ALL therapy over the last several decades, with significant improvements in prognosis for patients with adult ALL. These successes are partially based on the progress in genetics and the incorporation of pharmacogenomics. New risk stratification, personalized regimens and therapeutic modification based upon insights into drug clearance ideally should be integrated with SNP genotypes and genetics testing to help us better predict therapy response and avoid drug toxicity. The FDA currently recommends genetic testing of *TPMT* for all patients who will be treated with high dose 6-MP in order to prevent hematopoietic toxicity. Despite these recommendations, the use of genetic testing to best individualize therapy is not universal. Among the barriers responsible for a failure to adopt such testing are inadequate recognition of the clinical benefits for patient care, high cost, concerns about the ethical implication of these data, and the technical challenges/availability of the tests. Additionally, pharmacogenomics alone will likely be insufficient to explain all of the variability. There may be some nihilism about the potential benefits of such testing. The application of pharmacogenomics remains a challenge; however these data support the proposition that this area warrants further research. We anticipate that in the future molecular profiles will help tailor individualized ALL therapy. Indeed, the future may be upon us since the group at St. Jude Children's Research Hospital have developed a systemic approach and incorporated pharmacogenetics testing, including *TPMT*, *CYP2D6*, *SLCO1B1* and *CYP2C19*, into their most recent prospective ALL protocol (PG4KDS), providing a model for what is possible in clinical practice [105].

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Table 1

Summary of pharmacogenomic studies of ALL treatment.

Drugs	Gene	Effect	Reference
L-asparaginase	*GRIA1*	hypersensitivity	[23]
	*HLA-DRB*0701*	hypersensitivity	[106]
	ASNS	resistance	[19, 20, 22]
	ATF5	relapse	[21]
Glucocorticoid	*IL-10*	drug efficacy	[31]
	GST	drug efficacy, infection	[32, 33]
	SWI/SNF	drug resistance	[34, 43]
	NOTCH pathway	drug sensitivity	[35]
	XIAP	drug resistance	[37]
	TBL1XR1	drug resistance	[107]
	EMP1	drug resistance	[108]
	CRHR1	osteoporosis	[41]
	TYMS	osteonecrosis	[44]
	PAI-1	osteonecrosis	[45]
	ACP1	osteonecrosis	[46]
	AHSG, IL-6, POLDIP3	sleep disturbance	[47]
6-MP	*TPMT*	myelosuppression, brain tumor	[50, 51]
	ITPA	drug clearance, toxicity	[53, 55–59]
MTX	*RFC-1/SLC19A1*	resistance	[61–64]
	SLCO1B1	GI toxicity, drug clearance	[65, 67–70]
	MTHFR	MTX level, neurotoxicity, relapse	[65, 72–77]
	TYMS	relapse	[79–81]
	DHFR	resistance	[82]
	ABCC	resistance	[83]
	DROSHA	GI toxicity	[84]
Vincristine	*CYP3A5*	neuropathy	[88]
	CEP72	neuropathy	[92]
TKIs	*IKZF1*	heterogeneous response	[96]
	CYP3A4/5	drug efficacy	[98, 99]
	*CYP2D6*4*	adverse effect	[101]
	ABCG2421A	adverse effect	[102]

GRIA1, glutamate AMPA receptor subunit 1 gene; *HLA*, human leukocyte antigen; *ASNS*, asparagines synthetase gene; *ATF5*, activating transcription factor 5 gene; *IL*, interleukin gene; *GST*, glutathione-S-transferase gene; *SWI/SNF*, SWItch/Sucrose Non Fermentable nucleosome complex gene; *XIAP*, X-linked inhibition of apoptosis protein gene; *TBL1XR1*, transducin beta-like 1 X-linked receptor 1 gene; *EMP1*, epithelial membrane protein 1 gene; *CRHR1*, corticotrophin-releasing hormone receptor 1 gene; *PAI-1*, plasminogen activator inhibitor-1; *ACP1*, acid phosphatase 1 gene; *AHSG*, alpha-2-HS-glycoprotein gene; *POLDIP3*, polymerase delta interacting protein 3 gene; *TPMT*, thiopurine methyltransferase gene; *ITPA*, inosine triphosphate pyrophosphatase gene; *RFC-1/SLC19A1*, reduced folate carrier 1 or solute carrier family 19 member 1 gene; *SLCO1B1*, solute carrier organic anion transporter 1B1 gene; *MTHFR*, methylenetetrahydrofolate reductase gene; *TYMS*, thymidylate synthase gene; *DHFR*, dihydrofolate reductase gene; *ABCC*, ATP-binding cassette sub-family C gene; *DROSHA*, RNAse III gene;

IKZF1, Ikaros family zinic finger protein 1 gene; *CYP*, cytochrome P450 enzymes gene; *ABCG*, ATP-binding cassette sub-family G gene; *CEP72*, centrosomal protein of 72 kDa.