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Pharmacogenomics in pediatric leukemia

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Abstract

Purpose of review—The therapeutic index of many medications, especially in children, is very narrow with substantial risk for toxicity at doses required for therapeutic effects. This is particularly relevant to cancer chemotherapy, where the risk of toxicity must be balanced against potential suboptimal (low) systemic exposure that can be less effective in patients with the higher rates of drug clearance. The purpose of this review is to discuss genetic factors that lead to interpatient differences in the pharmacokinetics and pharmacodynamics of these medications.

Recent findings—Genome wide agonistic studies of pediatric patient populations are revealing genome variations that may affect susceptibility to specific diseases and that influence the pharmacokinetic and pharmacodynamic characteristics of medications. Several genetic factors with relatively small effect may be combined in the determination of a pharmacogenomic phenotype and considering these polygenic models may be mandatory in order to predict the related drug response phenotypes. These findings have potential to yield new insights into disease pathogenesis, and lead to molecular diagnostics that can be used to optimize the treatment of childhood cancers

Summary—Advances in genome technology and their comprehensive and systematic deployment to elucidate the genomic basis of inter-patient differences in drug response and disease risk, hold great promise to ultimately enhance the efficacy and reduce the toxicity of drug therapy in children.

Keywords

pharmacogenomics; pharmacokinetics; pharmacodynamics; leukemia

Introduction

Pharmacogenomics is the study of the genomic basis for interindividual differences in the absorption, distribution, metabolism, excretion of drugs (pharmacokinetics) and the relationship to pharmacologic effects, either therapeutic or adverse (pharmacodynamics). Broad interpatient variability is seen in response to many medications and for drugs with a narrow therapeutic index (including most cancer chemotherapy) there is increased risk for adverse reactions or suboptimal systemic exposure at doses required for therapeutic effects [1]. These pharmacokinetic differences can be caused by genetic differences (inherited or acquired) or environmental differences (e.g. drug interactions) among patients.

More comprehensive and higher resolution analyses of patient populations, including whole genome sequencing [2], will continue to enhance the identification of genome variations influencing drug response, which will ultimately improve the use of medications in humans.

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The management of genetic results that are initially incidental, but potentially highly relevant in future contexts needs to be addressed in order to realize the promise of genetics based personalized medicine [3].

Genetic susceptibility to pediatric ALL and response to treatment

Treatment response, overall outcome or event free survival of pediatric ALL patients has been linked in several studies to host genome polymorphisms as well as acquired genome variations in leukemia cells. Genome wide analysis of single nucleotide polymorphisms (SNPs) in germline DNA revealed that polymorphisms in the AT rich interactive domain 5B gene (ARID5B) and IKAROS family zinc finger 1 gene (IKZF1) had allele frequencies that differed significantly between pediatric ALL cases and non-ALL controls [4, 5]. In the two independent studies, an odds ratio of 1.91 and 1.65 were seen for ARID5B SNPs distinguishing ALL cases and non-ALL controls [4, 5]. Polymorphisms in ARID5B also distinguished B-hyperdiploid ALL from other subtypes in two separate cohorts. Interestingly the ARID5B SNPs were also associated with methotrexate accumulation and gene expression pattern in B-hyperdiploid leukemic lymphoblasts, reasonably connecting these genotypes to drug response [4]. In a separate study, germline SNPs that were associated with minimal residual disease in two independent cohorts of children with newly diagnosed ALL were described. Five of the 102 SNPs identified occurred in the interleukin 15 (IL15), a cytokine associated with activation and proliferation of hematopoietic cells [6].

Focused candidate gene approaches have also yielded genotypes predictive of hematologic relapse in high-risk ALL patients. High-risk patients with the glutathione S-transferase (GSTM1) non-null genotype had greater risk of hematologic relapse and this effect was even greater in patients inheriting the thymidylate synthetase (TYMS) 3/3 genotype; both genotypes remained predictive of hematologic relapse in multivariate analyses [7].

6-Mercaptopurine

6-Mercaptopurine (6MP) is metabolized to thioinosine monophosphate and eventually to mono-, di-, and triphosphates of 6-thioguanosine by a series of enzymes, with the initial step catalyzed by hypoxanthine phosphoribosyl transferase (HPRT). These metabolites, which are collectively termed 6-thioguanine nucleotides (TGNs), interfere with normal DNA and RNA synthesis and are critical for the cytotoxic effects of 6MP[8]. 6MP can also be methylated by thiopurine methyltransferase (TPMT) to methylmercaptopurine[9–11] an inactive metabolite that cannot be converted to active nucleotides. 6MP can also be catabolized by xanthine oxidase to inactive thiouric acid. Additionally, 6-thioinosine monophosphate is a substrate for TPMT, and the methylated derivative is able to inhibit de novo purine synthesis [12, 13].

TPMT is encoded by a gene that presents non-synonymous SNPs associated with reduced TPMT activity and important clinical implications (Figure 1). Approximately one out of every five hundred people inherit two non-functional variants of the TPMT gene, 5–7% are heterozygous, and the rest are homozygous wild-type in the majority of world populations studied thus far [19–24]. Those who inherit a non-functional variant allele and a wildtype allele (i.e. heterozygotes) are more likely to require a dose reduction to avoid acute myelosuppression [14] than are wild-type patients, but not the dramatic dose reduction (10-fold) required in TPMT-deficient patients. Even when 6MP dosage is significantly reduced in TPMT deficient patients (as little as 5–10% of the standard dosage, or 10–30 mg/m² orally 3 days/week), the RBC TGN level tends to stay higher (1000–3000 pmol/8×10⁸ RBCs) than the population median [25] and their treatment outcome is not compromised [17].

TPMT deficiency based on molecular diagnosis of the most common inactivating SNPs [26–29] is now used to prospectively identify patients at higher risk of 6MP hematopoietic toxicity. Both phenotype (TPMT activity in RBCs) and genotype can be used to diagnose TPMT deficiency in patients, but patient identification based on genotype has the benefit of circumventing the confounding effects of allogeneic erythrocyte transfusions that can cause spuriously high TPMT enzyme activity in patients who have received a RBC transfusion [30]. The diagnosis of TPMT deficiency allows for the rational reduction of 6MP dosages while other concurrent cytotoxic agents remain at their usual unadjusted doses.

Besides TPMT, other genetic factors may influence the effects of mercaptopurine, even if their clinical relevance is less characterized. A recent study showed that as treatment is individualized for TPMT, the most relevant genetic determinant of drug response for mercaptopurine, the importance of other genetic polymorphisms in enzymes involved in mercaptopurine metabolism (e.g.: inosine triphosphate pyrophosphatase, ITPA) emerges: there was a significantly higher probability of severe febrile neutropenia in patients with a variant ITPA allele among patients whose dose of mercaptopurine had been adjusted for TPMT genotype. In a cohort of patients whose mercaptopurine dose was not adjusted for TPMT phenotype, the TPMT genotype had a greater effect than the ITPA genotype [16]. Other studies have shown that genetic features modulating expression or activity of nucleosides transporters (i.e., MRP4 or SLC29A1), cause intracellular accumulation of the active metabolites of mercaptopurine [31–33].

Methotrexate

A prodrug requiring intracellular polyglutamation for maximum cytotoxic effects [34–37], methotrexate (MTX) is extensively used in leukemia chemotherapy. Folylpolyglutamate synthetase (FPGS) is responsible for the activation of MTX to MTX-polyglutamates, and has been shown to sequentially add up to as many as five glutamates to MTX, both *in vitro* [38, 39] and *in vivo* in leukemia lymphoblasts [40, 41]. MTXPG formation is considered beneficial as these metabolites cause greater inhibition of target enzymes (e.g. dihydrofolate reductase, TYMS) and those with longer polyglutamate chains are retained longer in cells compared to MTX [35, 36, 42, 43]. Mechanisms influencing the relative sensitivity or resistance of cancer cells to MTX include impairment of MTX entry into cells via the reduced folate carrier [44], decreased formation of MTXPG due to low folylpolyglutamate synthetase activity (FPGS) [45–47], increased hydrolysis of MTXPG via gamma glutamyl hydrolase (GGH) [48] and enhanced efflux of MTX from cells via ABCG2 or ABCC1 [49]. Oligonucleotide microarrays allowed the identification of gene signatures associated with reduction of circulating leukemia cells after initial *in vivo* treatment with MTX [50]; folate-pathway oriented analysis using led to the identification of the molecular causes of ALL-subtype specific differences in MTXPG accumulation [51]. A recent genome-wide study was aimed at characterizing how inheritance affects methotrexate pharmacokinetics in pediatric patients with ALL: this study identified and validated SNPs in the organic anion transporter polypeptide, SLCO1B1 as determinants of methotrexate clearance and also associated with methotrexate-induced GI toxicity [52].

Glucocorticoids

Commonly used in induction, reinduction, and continuation drug regimens, dexamethasone and prednisone serve as “cornerstone” drugs for the treatment of childhood ALL. Prednisone doses of about 40 mg/m² per day of and dexamethasone doses of 6 to 8 mg/m² per day of have generally been used in ALL regimens. The equipotent clinical dosages of dexamethasone and prednisone is unclear, and depends on the pharmacodynamic endpoint used for comparison. Randomized studies show improved cure rates with dexamethasone

compared to prednisone [53–55]. Prospective trials evaluating the two agents in standard-risk B-lineage ALL showed that dexamethasone at 6 mg/m² resulted in improved event-free survival compared to prednisone 40 mg/m² [56, 57] and other studies have shown that fewer CNS relapses occurred in a group treated with similar doses of dexamethasone and prednisone [55]. Dexamethasone's toxicity relative to prednisone is not entirely clear, but increased toxic death rates have been reported with some remission induction regimens that include dexamethasone [58]. The dose of dexamethasone relative to an equipotent dose of prednisone, along with concomitant therapy, are likely to influence differences in toxicity, as many have safely used dexamethasone [53–55, 59]. To elucidate the molecular bases of glucocorticoids resistance in ALL, *in vitro* sensitivity to prednisolone was employed to identify gene expression patterns related with glucocorticoids resistance [60]. This study led to the identification of lower expression of a core member of the SWI/SFI complex, SMARCB1 as strongly associated with GC resistance in ALL cells. The effect of SMARCB1 was confirmed by an *in vitro* study on cellular models; moreover, subsequent study performed on two independent cohorts of ALL patients, showed decreased expression of other key members of the SWI/SFI complex as significantly related to GC resistance, providing consistent evidence that defects in the SWI/SFI chromatin remodeling complexes of ALL cells can confer resistance to GC [61, 62].

Asparaginase

Asparaginase exploits a metabolic difference between normal and leukemic cells as normal cells are able to synthesize most amino acids (including asparagines), however some leukemic cells are unable to induce the enzyme asparagine synthetase in response to asparagine depletion [63]. Asparaginase is an effective chemotherapeutic agent in childhood ALL and therefore a component in most multiagent remission induction regimens [64]. Unlike most other chemotherapy agents, asparaginase does not enter cells, but deprives leukemic cells of their source of asparagine by working extracellularly to hydrolyze asparagine to aspartic acid and ammonia.

Different preparations of asparaginase have different pharmacokinetic properties [63, 65–67]. Asparaginase is isolated from various natural sources: *Escherichia coli* and *Erwinia chrysanthemi* and PEG-asparaginase is where native *E. coli* asparaginase has been covalently linked to polyethylene glycol (PEG) at sites not affecting enzymatic activity. The PEGylation of asparaginase prolongs the elimination half-life of the drug and decreasing the probability of developing antibodies against the asparaginase by preventing uptake by the reticuloendothelial system [68].

As many as seventy percent of patients may develop anti-asparaginase antibodies, many without clinical evidence of hypersensitivity [69, 70]. Antibody levels are higher, both before and after the occurrence of the reaction, in patients who develop clinical hypersensitivity to asparaginase. Also, antibody concentrations increase in patients receiving asparaginase over time, regardless of whether patients exhibit clinical allergy [71, 72]. It has been suggested that these antibodies may hamper the antileukemic effect of asparaginase by shortening its half-life, preventing or delaying absorption after intramuscular injection, or interfering with enzymatic activity [69, 73, 74]. However, it has been reported that development of antibodies or hypersensitivity to asparaginase did not appear to impact treatment outcome of childhood acute lymphoblastic leukemia [75].

Anthracyclines

Both daunorubicin and doxorubicin have similar pharmacokinetic properties and exhibit long terminal plasma half-lives with extensive tissue binding. With the exception of the central nervous system these drugs penetrate into tissues rapidly during the distributive

phase and plasma drug concentrations decline rapidly as the drug is absorbed and binds DNA. Daunorubicin and doxorubicin can both be metabolized by the cytosolic aldo/keto reductases [76, 77] to form their 13-hydroxylated metabolites, and doxorubicinol respectively. The majority of daunorubicin systemic exposure is to its 13-hydroxylated metabolite, which distinguishes it from doxorubicin for which doxorubicinol concentrations are generally below those of doxorubicin [78]. The peak plasma concentrations are similar in adults and children, but [79] daunorubicinol has about 10% the cytotoxic activity of daunorubicin in bone marrow stem cells [80], and doxorubicinol has approximately 5% of the anti-tumor activity of doxorubicin [81], but may be a more potent cardiotoxin [82]. Newer anthracyclines, (e.g. idarubicin, liposomal daunorubicin or doxorubicin) may be associated with reduction of cardiotoxic effects [83–85]. To what extent the degree of anthracycline exposure with each individual dosage, versus cumulative dosage, contributes to an increased risk of anthracycline cardiotoxicity is unresolved. A recent genome-wide study attempted the identification of genomic determinants for daunorubicin sensitivity using an *in vitro* cell-line based pharmacological system: SNPs identified predicted 29% of the overall variation in daunorubicin sensitivity and the expression of CYP1B1 was significantly correlated with sensitivity to daunorubicin; this study needs validation on ALL patients' populations but may provide insights on genetic variants contributing to daunorubicin clinical effects [86].

Vincristine

Knowledge of vincristine pharmacokinetics and pharmacodynamics is limited in part due to difficulties in quantitating the low plasma concentrations of the drug. Both interindividual and intraindividual variability is seen in vincristine pharmacokinetics in children [87, 88] possibly connected to transporter-mediated excretion or steroid induction of P450 metabolism [89]. Phenytoin and carbamazepine are also known to interact with vincristine as they can induce CYP3A4 expression and therefore increase vincristine clearance [90]. Substitutes to enzyme-inducing anticonvulsants should be considered for chemotherapy receiving ALL patients as long-term anticonvulsant therapy has been linked to lower efficacy of chemotherapy and increases the systemic clearance of several antileukemic agents [91]. Inter-racial differences in allele frequencies of CYP3A4, CYP3A5, and MDR1 polymorphisms have been reported, [92–94] and may affect both the desired and adverse response to vincristine [95].

Patients with an elevated alkaline phosphatase more frequently see increased neurotoxicity [96], dosage reductions have been recommended for patients with hepatic obstruction as biliary excretion is responsible for a large portion of vincristine clearance [97]. More current studies did not see a clear link between neurotoxicity and vincristine AUC in pediatric patients, when vincristine is measured using a more accurate HPLC based assay [98]. Whether the high frequency of neurotoxicity in very young infants (frequently necessitating lower dosages) was due to poor drug clearance or to increased tissue sensitivity is not known.

Cytarabine

Cytarabine (ara-C) is a prodrug which requires its intracellular phosphorylation by deoxycytidine kinase (dCK) to produce its active form, 1- β -D-arabinofuranosyl cytosine-5'-triphosphate (ara-CTP) and chemotherapeutic regimens for acute leukemias have included (ara-C) for more than 40 years [99]. Cytarabine's mechanism of action is thought to be due to both inhibition of DNA polymerase and its incorporation into DNA leading to chain termination, thereby blocking DNA synthesis. Deoxycytidine kinase has had greater than 60 genetic variations identified, including 3 non-synonymous coding changes [100] and

decreased expression or activity of dCK has been reported as a mechanism responsible for clinical resistance [101–103]. Inactivating enzymes of ara-C including cytidine deaminase or 5'-nucleotidase have also been correlated with outcome [103–106]. Uptake by cells at standard doses (~100 mg/m²) is mediated by facilitated diffusion and depends on the number of transmembranous nucleoside carrier sites [107]. Gene expression of human equilibrative nucleoside transporter 1 (hENT1) has been positively associated with intracellular accumulation of ara-CTP in patients with AML being treated with ara-C [108]. Uptake and intracellular phosphorylation are critical for the cytotoxicity of cytarabine [109].

Conclusion

There are now several examples of pharmacogenomic tests that have clear utility in identifying patients who are at high risk of developing drug toxicity or who are less likely to derive full therapeutic effects from a medication: the US FDA internet site reports a constantly updated comprehensive list of valid genomic biomarkers in the context of approved drug labels [110]. The best examples of clear clinical utility include thiopurine therapy and the *TPMT* genetic polymorphism [14, 111, 112], warfarin and *CYP2C9* & *VKORC1* [113], irinotecan and *UGT1A1* [114], clopidogrel and *CYP2C19* [115] and codeine and *CYP2D6* [116, 117]; the FDA product label for each of these medications now includes information about pharmacogenetic testing. There are several others, such as HMG-CoA reductase inhibitors (i.e., “statins”) and *SLC01B* [118] or *ribavirin* and *ITPA* [2, 119], that are clearly important, but have not yet been included in the FDA product label. Yet the use of genetic tests to individualize drug therapy is not a universal component of healthcare, even for those medications where it is included in the product label [3]. Reasons for slow adaptation of pharmacogenetic tests in the clinic include the lack of readily available CLIA-certified genotyping methods/labs for many of these genes, the lack of widespread understanding among clinicians of how best to use pharmacogenetic tests in patient care, and concerns about collateral implications of some pharmacogenetic genotypes (i.e., when a genetic test for a medication also has implications for disease risk unrelated to its pharmacogenetic utility). Some argue that the absence of randomized trials documenting clinical benefits and the paucity of studies showing cost-benefit are also forces working against the widespread clinical use of pharmacogenetic tests. This may be true, although the absence of such studies has not precluded the clinical use of proton beam radiation therapy or diagnostics such as PET-CT scans. Perhaps the overarching issues of genetic exceptionalism [3] are also working against broad adaptation, even though genetic non-discrimination laws mitigate most legal arguments against incorporating genetic test into clinical practice and the medical record. Clearly, genotyping is becoming easier and less expensive (i.e., currently >1900 genotypes in >200 pharmacogenetic genes can be performed with the Affymetrix DMET chip, using only 1 µg of DNA for around \$300), and clinical trials are establishing more fully the benefits of pharmacogenetic tests, so it is just a matter of time before this becomes a routine diagnostic for individualizing drug therapy. Performing these tests early in childhood will provide a lifetime of benefit and should one day become the norm.

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Figure 1.

Adjustment of mercaptopurine therapy on the basis of TPMT status allows reduction in toxicity with no decrease in efficacy. The upper panels depict the predominant TPMT variant alleles causing autosomal codominant inheritance of TPMT activity in humans. As depicted in the subsequent lower panels, when uniform conventional body surface based dosing of thiopurine medications are applied to patients, TPMT-deficient patients accumulate marked higher (10-fold) cellular concentrations of the active thioguanine nucleotides (TGN) and heterozygous patients accumulate approximately two-fold higher TGN concentrations, determining a significantly higher frequency of toxicity (lower left panel). As depicted in the lower right panel, personalization of therapy of mercaptopurine according to TPMT status, integrating assessment of TPMT genotype, TPMT activity and TGN levels, comparable cellular TGN concentrations are achieved and all three TPMT phenotypes can be treated without acute toxicity [14–16]. Mercaptopurine individualized

dosing has no detrimental effect on the efficacy of therapy [17]. At St. Jude Children's Research Hospital, in the current treatment protocol for ALL, TPMT status is assessed in all patients as follows in order to individualize mercaptopurine dosing: TPMT genotype is assessed at diagnosis, while TPMT activity and TGN are measured at start of reinduction therapies; TGN and TPMT activity are measured subsequently in patients with high TGN level, suspected noncompliance, problems with toxicities or high blood counts. Figure modified with permission from Evans, 2002 [18].