PHARMACOGENOMICS OF SERIOUS ADVERSE DRUG REACTIONS IN PEDIATRIC ONCOLOGY

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ABSTRACT

Adverse drug reactions (ADRs) rank as one of the top ten leading causes of death and illness in the developed world. In cancer therapy, more patients are surviving cancer than ever before, but 40% of cancer survivors suffer life-threatening or permanently disabling severe ADRs and are left with long-term sequelae. ADRs are often more frequent and more severe in children, and the consequences for children who experience a severe ADR can be catastrophic. Pharmacogenomics has the potential to improve the safety of these drugs. This review highlights severe ADRs that can occur in cancer therapy that are more frequent and more severe in children, and the pharmacogenomics research that aims to understand, predict, and ultimately prevent these severe reactions.

Key Words: *Adverse drug reactions, pharmacogenomics, pediatric, oncology*

Severe Adverse Drug Reactions in Children with Cancer

The paradox of modern drug development is that clinical trials provide evidence about efficacy and preliminary safety at standardized doses in large populations, while physicians treat individual patients who often differ in their response to drug therapies. Some patients will develop a severe adverse drug reaction (ADR), a potentially life-threatening or permanently disabling effect that is caused directly by a medication, even though the medication is administered at a normal recommended dose. The debilitating and lethal consequences of severe ADRs are a major problem in modern medicine. In the USA and UK, ADRs account for an alarming 7% of all hospital admissions.[1,2] ADRs are ranked as the 5th leading cause of death in the USA, and cause over 2 million severe reactions and claim 100,000-218,000 lives annually, and cost over $100 billion dollars each year.[2-5]

For children with cancer, ADRs are a very serious problem. More pediatric cancer patients are surviving cancer than ever before, with 5 year survival rates greater than 82%.[6] However, this has led to a striking increase in the long-term burden of adverse reactions to cancer therapy. Nearly three quarters of cancer survivors suffer an ADR related to their cancer therapy.[7] ADRs are often more frequent and more severe in children. Of all hospital admissions for pediatric cancer patients, 22% are caused by ADRs.[8] The consequences for children who experience a severe ADR can be catastrophic. While some ADRs result in treatment cessation or reduced adherence to needed medications, 40% of cancer survivors have suffered a severe life-threatening or permanently disabling ADR, and are left with long-term sequelae.[7] This review focuses on severe ADRs in children being treated for cancer and a review of the research to identify genetic susceptibility factors to these severe reactions.

Pharmacogenomics to Reduce the Occurrence of Severe ADRs

Although many factors influence the effect of medications (i.e. age, organ function, and drug interactions), genetic factors often account for a significant proportion of drug response variability.[5,9-12] In many cases, a prime determinant of drug toxicity is an agent's concentration at the drug target site or in plasma. The effective concentration of a drug depends on its absorption, distribution, metabolism and elimination. Genetic variations in drug-metabolizing enzymes and drug transport systems may lead to large differences in drug exposure between individuals resulting in toxicity or ineffective drug treatment in significant numbers of patients.[13,14]

The goal of pharmacogenomics is to avoid adverse drug reactions and maximize drug efficacy for individual patients. Pharmacogenomic studies are performed in populations of subjects treated with a specific drug to identify genetic variants that predict drug response or the occurrence of adverse reactions. Once identified and validated, a genetic variant can be incorporated into a diagnostic test that will predict a patient's response to the specific drug. Pharmacogenomics may improve the benefits and reduce the risks of medications by determining which patients are most likely to respond favourably to a specific medication and by predicting in whom there is a greater risk for an adverse drug reaction.[15]

Unlike other factors influencing drug response, inherited determinants remain stable throughout a person's lifetime and provide an unprecedented means to predict and prevent serious ADRs. The culmination of landmark scientific advances such as sequencing the human genome, the International HapMap project, and new technologies for accurate and efficient high-throughput genotyping and sequencing have created an opportunity to make DNA-based testing for drug safety a reality. Examples of diagnostic tests to guide pharmacotherapy in adult cancer patients include tests for *UGT1A1* variants for life-threatening irinotecan-induced toxicity,[16,17] *TPMT* variants to prevent potentially lethal azathioprine-myelosuppression,[18,19] *CYP2D6* for tamoxifen efficacy,[20,21] and *CYP2C9* and *VKORC1* variants to guide warfarin dosing.[22,23] These tests are recommended by the FDA, and "point of care" testing for these markers may soon be widely available once cost-effective test methodology is established.

Thiopurine-induced Myelotoxicity

In children with acute lymphoblastic leukemia (ALL), the thiopurines mercaptopurine (6-MP) and thioguanine (6-TG) are frequently used for treatment. Thiopurines are normally administered as a daily oral dose for up to two and a half years of maintenance therapy. However, some patients suffer hematopoietic toxicity to thiopurines causing severe myelosuppression. Consequently patients are routinely monitored for blood cell counts.

The pharmacogenetics of thiopurine myelotoxicity are partly explained by genetic variants in the thiopurine S-methyltransferase (*TPMT*) gene. Thiopurine drugs are inactive prodrugs that undergo a multistep activation into thioguanine nucleotides (TGN). The TGN exert their cytotoxicity through incorporation into DNA and RNA and inhibition of *de novo* purine synthesis.[18,24-26] The cellular accumulation of active TGN is inversely related to TPMT activity levels, because TPMT inactivates intermediate thiopurine metabolites, thereby reducing the levels of active TGN. However, approximately 10% of people have reduced TPMT activity levels, and 0.3% of people have no detectable TPMT enzyme activity, because they inherit one or two *TPMT* genetic variants that eliminate TPMT enzyme activity.[18,25-27] More than 20 variant alleles of *TPMT* with decreased TPMT activity have now been identified,[28] and more than 95% of defective TPMT activity is due to the most frequent mutant alleles, *TPMT**2 and *TPMT**3A-D. TPMT-deficient patients accumulate higher concentrations of active TGN and suffer severe, and in some cases lethal, myelotoxicity, and frequently discontinue therapy unless the thiopurine dose is reduced 10-15-fold.[29-31]

In 2004, the FDA revised the thiopurine drug label to include information about the increased risk of severe adverse events caused by *TPMT* genetic variants.[32] This label change also applies to children because the pharmacogenetics of thiopurine myelotoxicity is one of the few severe

ADRs in oncology that has been directly studied in children.[33-35]

It is clear that *TPMT* variants alone do not account for all thiopurine toxicity. In fact, *TPMT* deficiency explains only a portion of myelotoxicity ADRs,[36] and is not predictive of other thiopurine ADRs including hepatotoxicity, pancreatitis, flu-like symptoms, nausea, vomiting, and rash.[37] Multiple enzymes are involved in the metabolism of thiopurine drugs to active or inactive forms, and functional genetic variants in this pathway could also contribute to thiopurine toxicity. Inosine triphosphate pyrophosphatase (*ITPA*) is one gene that has been investigated in the thiopurine pathway. However, in a meta-analysis of patients with inflammatory bowel disease, a variant in *ITPA* (Pro32Thr, rs1127354) that abolishes *ITPA* enzymatic activity was found not to be associated with thiopurine toxicity.[38] In a more recent study of children with ALL where *TPMT* genotype was also taken into account and used to adjust patient thiopurine doses, the *ITPA* variant was significantly associated with severe neutropenia (odds ratio (OR) 2.98, P-value 0.018).[36] As the genetic factors influencing thiopurine toxicity are further elucidated, new diagnostic tests will likely be developed that evaluate the cumulative effect of multiple genetic variants on thiopurine use on a child-by-child basis.[37]

Vincristine-induced Peripheral Neuropathy

Vincristine is considered the backbone chemotherapeutic agent for many blood and solid malignancies. Vincristine is a natural alkaloid isolated that interferes with the assembly of microtubule structures to effectively kill rapidly dividing cells. However, peripheral neuropathy is a frequently dose-limiting serious ADR to vincristine which occurs in 4% to 28% of children.[39]

The symptoms of neuropathy include paresthesias, burning and "shock-like" sensations, stabbing pain, ataxia, muscle weakness, orthostatic hypotension, bowel dysmotility, and vocal cord paralysis.[40] In some cases, neuropathy is responsible for altering dose regimens or stopping vincristine anti-tumor therapy. Vincristine neuropathy frequently causes a significant impairment in day-to-day activities, and may also lead to anxiety and depression, and in severe cases can be lethal.[41-43] Severe acute reactions such as vocal cord paralysis can require emergency intubation and the need for long term tracheostomy with prolonged mechanical ventilation.[44] There are currently no effective strategies to prevent vincristine-induced peripheral neuropathy other than the treatment of symptomatic pain with high dose opioids.[45-47]

The mechanism of vincristine peripheral neuropathy has not been fully elucidated. Vincristine peripheral neuropathy appears to be a dose-dependent reaction with peak plasma vincristine concentrations correlating with peripheral neuropathy.[47-50] However, some patients are susceptible at any dose, and there is a dramatic 19-fold variability in peak plasma vincristine levels in children as well as large inter-racial differences in vincristine toxicity and response rates. This suggests that genetic factors may play an important role in individual susceptibility to vincristine-induced peripheral neuropathy.[51-55]

The biotransformation of vincristine is primarily catalyzed by CYP3A5, and to a lesser extent by CYP3A4.[56] *CYP3A5* is highly polymorphic and is not expressed in 20% of Africans and 80% of Caucasians.[57] Single nucleotide polymorphisms (SNPs) in *CYP3A5* (*CYP3A5**3 and *CYP3A5**6) cause alternative splicing and protein truncation, resulting in the absence of CYP3A5 activity.[58] CYP3A5 non-expressers have a 5-fold reduced clearance of vincristine which could significantly increase the risk of vincristine toxicity.[57] In line with this, a study investigating the effect of race on vincristine neurotoxicity found that African-Americans have a more than 7-fold lower rate of neurotoxicity compared to Caucasians.[59] Furthermore, a recent study looking at drug toxicity in pediatric ALL patients receiving vincristine found that variants in *CYP3A5* (*3) and the vitamin D receptor (VDR), which regulates *CYP3A4*, *CYP3A5*, and *ABCB1*, are associated with peripheral neuropathy.[60]

Vincristine is exported from cells by the ABCC1 transporter.[56] Expression of ABCC1 in cancer cells has been associated with reduced accumulation and *in vitro* resistance to vincristine. Additionally, P-glycoprotein (ABCB1) may also

be involved in the vincristine export from cells.[61]

Vincristine neuropathy may be caused by demyelination, which occurs in cell lines and animals exposed to vincristine.[62] There is a significantly greater risk of severe vincristine toxicity in patients with pre-existing peripheral neuropathy or with the demyelinating form of Charcot Marie Tooth disease (type 1A), an autosomal dominant disease caused by a duplication of the peripheral myelin protein 22 (*PMP22*).[63] On the other hand, some genetic variants in the gene encoding gap junction protein beta 1 (*GJB1*) may improve the tolerance of vincristine without adverse effects.[39,64]

Thus far, no genetic variants have been conclusively validated to be involved in vincristine-induced neuropathy and no diagnostic tests have been developed.[65] In the future, a pharmacogenetic test to identify those patients at highest risk could significantly improve treatment outcomes for children who receive vincristine.

Cisplatin-induced Ototoxicity, Neurotoxicity, and Nephrotoxicity

Cisplatin is a highly effective chemotherapeutic that binds and alkylates DNA.[66] Cisplatin is widely used throughout the world; however, the use of cisplatin is significantly restricted by the high incidence of severe toxicities, including irreversible hearing loss (ototoxicity), peripheral neurotoxicity, and nephrotoxicity.[67-70] Nephrotoxicity affects up to 20% of patients receiving cisplatin, culminating in the loss of renal function and triggering acute renal failure.[69] Acute and chronic neurotoxicity affects 15-60% of patients, causing paresthesias, areflexia, loss of proprioception and vibratory sensation, and loss of motor function.[68,70] Cisplatin has also been described as one of the most ototoxic drugs in clinical use, causing severe, permanent, bilateral hearing loss in 41-61% of children.[71-76] and 10-25% of adults.[75,77-79] Even mild losses of high-frequency hearing considerably increase a child's risk of learning difficulties and social-emotional problems.[74,80] Adverse reactions to cisplatin in children frequently lead to dose reduction and premature termination of cisplatin treatment, which may affect overall patient survival.[81]

The significant inter-individual variation in cisplatin toxicity is suggestive of genetic variation in drug metabolizing enzymes that render them especially susceptible to cisplatin adverse reactions.[82] Oxidative stress has been implicated in cisplatin ototoxicity[83] and the glutathione S-transferase (*GST*) gene family encodes isoenzymes that appear to be critical in protection against oxidative stress. Certain GST genes have null alleles (*GSTM1* and *GSTT1*), encode low-activity variants (*GSTP1*), or are associated with variable inducibility (*GSTM3*). One study identified a variant *GSTM3**B, that protects against cisplatin-ototoxicity (allelic OR 8.8, P = 0.02), although authors noted that the frequency of the *GSTM3**B polymorphism was too low to be a major factor regarding the susceptibility to cisplatin-induced hearing loss.[84] The authors did not find associations for variants in *GSTM1*, *GSTP1*, *GSTT1*, and *GSTZ1*.[84] More recently, in a larger study of 173 patients, specific genotypes of *GSTP1* and *GSTM1* were associated with cisplatin-ototoxicity.[85] The *GSTP1* "G/G", (Val/Val) form of the Ile105Val polymorphism (rs1695) was protective against hearing loss (OR 4.2, P < 0.001), while the presence of the *GSTM1* gene was associated with more severe hearing loss (OR 2.3, P = 0.02). The protective effects of *GSTP1* were unexpected, because the ^{105}Val-*GSTP1* variant is normally less effective in detoxifying cytotoxic drugs, however, the ^{105}Val-*GSTP1* variant was found to specifically protect against cisplatin cytotoxicity in E.Coli compared to the ^{105}Ile-*GSTP1* variant.[86]

Aminoglycosides exhibit similar nephrotoxicity and ototoxicity as cisplatin, and since deficiency of megalin was found to protect from renal aminoglycoside accumulation,[87] variants in the megalin gene were examined for association with cisplatin ototoxicity. In a study of 50 patients, the megalin Glu4094Lys variant (rs2075252) was associated with hearing impairment after cisplatin therapy (allelic OR 3.45, P = 0.02). The authors noted, however, that this finding requires further validation.

The impact of deafness-related genes in cisplatin-ototoxicity was recently explored in a pilot study of 11 survivors of childhood cancer who developed severe ototoxicity after cumulative cisplatin doses of less than 400 mg/m^2. However, no associations were found with the three mitochondrial DNA mutations known to be associated with aminoglycoside-

ototoxicity and high-frequency sensorineural hearing loss (A1555C, A3243G and A7445G), nor in the *SLC26A4* or *GJB2* (connexin 26) genes, which together are responsible for more than 30% of childhood congenital deafness.[88,89]

Variations in the *ERCC2* gene, which is involved in DNA damage repair, have been reported to be associated with tumour response to cisplatin. Eighty percent of the patients with the *ERCC2* Lys751Gln "TT" genotype (Lys/Lys) variant exhibited a greater response to cisplatin (characterized as more than 90% tumour necrosis), compared to a 45% response rate in patients that carried at least one "G" (Gln) allele (OR = 4.9, multiple test corrected P-value=0.047).[90] Similarly, patients with the "TT" genotype had a longer event free survival (240 months) compared to patients that carried at least one "G" (Gln) allele (184 months) (hazard ratio=5.8, P-value=0.021).[90]

As an alternative to using patients with cisplatin-ototoxicity, Dolan *et al*. used EBV-transformed B-lymphoblastoid cell lines from Centre d'Etude du Polymorphisme Humain (CEPH) pedigrees to show that sensitivity to cisplatin cytotoxicity is under significant genetic influence, and identified the strongest genetic signal near the ephrin receptor A2 (*EPHA2*) gene on chromosome 1.[91] The function of *EPHA2* is not well understood, but likely has a role in developmental events in the nervous system. Subsequent analyses of HapMap sample trios and 27 extended CEPH pedigrees that looked at cisplatin-induced inhibition of cell growth and incorporated RNA expression data to refine the analysis to functional variants, revealed new associations, including 10 SNPs located in five genes (*CDH13, ZNF659, LRRC3B, PITX2, and LARP2*), and 10 intergenic SNPs.[92,93] The authors acknowledged that this *in vitro* system has clear limitations, such as the single lymphoblast cell-type, the changes induced by EBV transformation, and limited *in vivo* applicability in humans, but this approach does provide a hypothesis generating system to identify potential targets to validate in larger association studies of patients that receive cisplatin.

We recently completed a Canada-wide study which identified genetic variants that cause cisplatin deafness in children.[94] In a B.C. Children's Hospital cohort of patients, we identified functional genetic variants in thiopurine S-methyltransferase (*TPMT*) and catechol O-methyltransferase (*COMT*). In a second Canada-wide replication study of 12 pediatric tertiary care hospitals, we confirmed the association of these variants with cisplatin-induced hearing loss (OR = 17.0, P-value 0.00022 and OR = 5.5, P-value = 0.00018 for *TPMT* and *COMT* respectively). Carrying these *TPMT* and/or *COMT* alleles significantly increases the risk of developing cisplatin-induced hearing loss.

Cisplatin ototoxicity is particularly severe and frequent in children, and although a definitive pharmacogenetic test is not currently available, these studies suggest that a test could be developed to assess a patient's genetic risk of cisplatin-induced toxicities in the future. The availability of a test to assess a patient's risk profile would open up opportunities for increased surveillance, alternate chemotherapies, or the use of currently experimental chemo-protectants and other preventative strategies in those patients at high risk.

Anthracycline Cardiotoxicity

Anthracyclines, such as doxorubicin and daunorubicin, are commonly used to treat childhood haematological malignancies such as ALL and lymphomas, as well as various solid tumors, such as osteosarcoma, Wilms' tumour, and hepatoblastoma. Nearly 60% of all childhood cancer patients receive anthracyclines[95] and their high effectiveness has contributed significantly to increases in childhood cancer survival rates. However, even though some patients can safely tolerate very high doses of anthracyclines (>1000 mg/m^2), up to 16% of patients will develop severe cardiotoxicity leading to congestive heart failure, some even at low doses (<300 mg/m^2).[96,97] Lipshultz *et al*. found that close to 60% of patients that received anthracyclines had some form of left ventricular structure or function abnormalities measured by echocardiogram.[98] At normal anthracycline doses nearly 6% of patients will eventually develop congestive heart failure, and almost 10% when treated with doses of 300 mg/m^2 or more.[95] This may lead to the requirement of heart transplantation or life-long treatment for chronic cardiac failure, with

mortality rates greater than 50%.[99] In addition, there is an increased risk in children less than 15 years, and an even higher risk in children less than 4 years of age.[97,100] These devastating effects can develop shortly after drug treatment, and may also occur many years after the completion of chemotherapy.[95]

The observed heterogeneity in anthracycline cardiotoxicity (ACT) may be explained by genetic susceptibility and gene-environment interactions. Elucidation of these factors could lead to more informed and patient-specific dosage individualization in the future. A uniform lowering of dose would reduce the risk of cardiotoxicity, but would be more than offset by increased cancer-related morbidity.

Even though anthracyclines have been extensively studied, controversy about the exact mechanisms of cardiac toxicity and the anti-cancer mechanisms remain. It is generally thought that anthracycline toxicity is caused by a combination of the generation of reactive oxygen species and the direct toxic effects of certain metabolites.[101] Many enzymes are involved in the metabolism and transportation of anthracyclines. Variations in enzyme efficiency or increased susceptibility to toxic metabolites due to genetic factors can be expected to increase the risk of cardiotoxicity. Apart from the wide variation in human sensitivity to the drug, there are also several *in vitro* and *in vivo* studies supporting this hypothesis. For example, overexpression of the multiple drug resistance gene (*Mdr1/Abcb1)* in mice protects them from ACT,[102] while knockout of the gene leads to increased accumulation of doxorubicin in the heart.[103] Overexpression of important anti-oxidant genes also protects mice from ACT,[104,105] while deficiency or overexpression of carbonyl reductase 1, a major doxorubicin-metabolizing enzyme, protects or enhances cardiotoxicity, respectively,[106,107] More recently, Huang *et al*. applied a similar unbiased genome-wide approach as earlier described for cisplatin, by looking at drug cytotoxicity in HapMap cell lines and showed a significant association between the expression of CYP1B1 and daunorubicin cytotoxicity.[108]

In addition to these *in vitro* and *in vivo* models, several studies in humans have reported the association of genetic variants with anthracycline cardiotoxicity.[109-112] Wojnowski *et al*. studied a subset of adult patients that had been treated for NHL. A total of 87 cases (44 acute and 43 chronic toxicity) and 363 well-matched controls were genotyped for 206 SNPs in 82 candidate genes with conceivable relevance to ACT. Acute toxicity was defined as arrhythmia, myocarditis-pericarditis, and acute heart failure during the first 3 cycles, and chronic toxicity was defined as heart failure after the third cycle or a reduction of the ejection fraction <50% or the fractional shortening <25%. They found 5 significant associations with polymorphisms in 3 subunits of the NAD(P)H oxidase (*NCF4*, *RAC2* and *CYBA)* involved in superoxide generation and in two doxorubicin transporters (*MRP1/ABCC1* and *MRP2/ABCC2*).[109] Only *NCF4* seemed to be specifically associated with chronic toxicity, while the others were associated with acute toxicity, and all variants were significant when acute and chronic cases were combined. To further verify the involvement of NAD(P)H oxidase, mice deficient for the gp91 subunit of NAD(P)H oxidase resulting in reduced oxidase activity were treated with doxorubicin and were shown to be protected from ACT. The association of *NCF4* (rs1883112) with cardiac toxicity was recently replicated in another study of 106 adults who were also treated for NHL.[112] In this study, 19 SNPs in 15 genes were tested for association with event-free survival as well as several toxicities; however the exact definition of cardiotoxicity was not provided. Only NCF4 rs1883112 remained significantly associated with cardiotoxicity in a multivariate analysis.[112] Whether the association of *NCF4* and ACT is specific to adults treated for NHL requires further study.

The first pediatric study used a nested case-control study design within the Childhood Cancer Survivor Study cohort.[110] Using questionnaires and interviews, study participants were ascertained for congestive heart failure (CHF). Thirty cases with CHF were matched with 115 controls and genotyped for the *NQO1*2* (rs1800566) and *CBR3* V244M polymorphism (rs1056892). No association was found between the *NQO1*2* variant and the risk of CHF. There was a trend toward association with the *CBR3* V244M polymorphism (OR=8.16, P=0.056 for G/G vs. A/A and OR=5.44, P=0.092 for G/A vs.

A/A) in multivariate analyses.[110] However, the authors state that larger follow-up studies are warranted. Another pediatric study focused on several genes involved in ROS metabolism.[111] Seventy-six patients treated for ALL during childhood, were evaluated for late cardiotoxicity defined by any abnormality found by echocardiography or electrocardiogram tracing. The study found an intronic variant (rs10836235) in catalase (CAT) to be associated with toxicity.[111] In contrast, a known functional variant in the promoter region of CAT was not significantly associated,[111] so these findings need further validation.

Warfarin-induced Bleeding and Thrombosis

Many pediatric patients are placed on warfarin for treatment of thrombotic events such as deep venous thrombosis or pulmonary emboli, or for the prevention of clots in cardiac patients with mechanical valves. Pediatric patients with cancer are at increased risk of developing deep venous thromboses at some point between diagnosis until the end of therapy causing significant morbidity and mortality.[113-115] Treatment of these blood clots with warfarin puts these children at an even higher risk for adverse events.[116] The stable therapeutic dose of warfarin for a pediatric patient is initially dosed based on the patient's weight with frequent monitoring of the International Normalized Ratio (INR), the blood test for warfarin, which needs to be performed to evaluate if warfarin is within its narrow therapeutic window. Typically, the dose is consistently adjusted up or down over the first few weeks based on the INR level.[117] Over or under-dosing of warfarin during this time can lead to serious risks of excessive bleeding including intracranial haemorrhage and the formation of additional blood clots.

Genetic polymorphisms in the cytochrome P450 (*CYP*) *2C9* gene and the vitamin K epoxide reductase complex 1 *(VKORC1)* significantly modulate adult patient responses to warfarin. CYP2C9 normally inactivates warfarin, and up to 20% of the population are carriers of low activity variants (*2 or *3). These patients require significantly lower doses of warfarin and are at higher risk for serious and life-threatening bleeding events, especially when dosed according to older, more traditional, algorithms.[118]

VKORC1 is a subunit of the enzyme that is repressed by warfarin to block blood coagulation. There are two conserved haplotypes of the *VKORC1* gene, defined by the -1639G/A variant.[119] "A" haplotype carriers require lower doses of warfarin while "G" haplotype carriers require higher doses.[119] These findings have been replicated, showing the clear effects of *CYP2C9* and *VKORC1*.[120] A recent genome-wide association study revealed that *VKORC1, CYP2C9*2* and *CYP2C9*3* account for nearly all of the genetic variation of warfarin dose, and identified one additional genetic variant in *CYP4F2*, Val433Met, which contributed to only 1.5% of overall warfarin dose requirements.[121]

A warfarin dosing algorithm for adult patients was recently validated by the International Warfarin Consortium[22] and the FDA modified the warfarin drug label to include pharmacogenetic information. The FDA has now approved four genetic tests for warfarin, including rapid tests that can provide results in less than 1 hour.[23] Preliminary reports have estimated that warfarin pharmacogenetic testing could prevent 17,000 strokes and 85,000 serious bleeding incidents and could save $1.1 billion in U.S. health care spending each year.[122]

In children, however, the coagulation system differs significantly from adults. In fact, the pediatric coagulation system is continually developing and changing over time and does not reach adult function until late adolescence.[123] It is not known if these genetic polymorphisms will have the same effect in children and if the warfarin pharmacogenetic dosing algorithm for adults will be applicable to pediatric patients.[124] In fact, the first small paediatric study looking at vitamin K agonists, including warfarin, revealed that age was the most important factor determining dose, accounting for 28% of variation in warfarin dose requirements, while *VKORC1* and *CYP2C9* genotypes had only minor roles (3.7% and 0.4% respectively) compared to approximately 40% and 8% in adult patients.[125]

Methotrexate-induced Nausea and Vomiting

Methotrexate disrupts endogenous cellular folate metabolism by inhibiting dihydrofolate reductase (DHFR) and blocking the metabolism of folic acid, thereby killing rapidly dividing cells by

blocking purine synthesis and the synthesis of DNA and RNA. High-dose methotrexate (dose 5-12 g/m^2) is increasingly used for the treatment of children with ALL, osteosarcoma, non-Hodgkin lymphoma (NHL), and brain tumours.[126] Methotrexate, however, may cause severe nausea, vomiting, leukencephalopathy, hepatitis and mucositis.

Cellular entry of methotrexate is mediated by *SLC19A1*. A common G/A non-synonymous variant in *SLC19A1* (His27Arg, rs1051266) is associated with a worse prognosis, as measured by event-free survival, for "A" carriers than "GG" carrier patients, and "AA" carrier patients have higher plasma levels of methotrexate.[127] Serious vomiting episodes, as defined by the presence of grade 2 symptoms or worse, occurred more frequently in individuals with an increasing number of "G" alleles.[128]

Methotrexate-induced Leukoencephalopathy

Some patients that receive methotrexate also develop severe leukoencephalopathy, defined as diffuse white matter injury, specifically not associated with focal necrosis. Acute and sub-acute toxic neurological effects have been observed after low or high doses of intrathecal or parenteral methotrexate administrations.[129] The morbidity of methotrexate-induced leukoencephalopathy ranges from mild to severe disseminated necrotizing leukoencephalopathy with severe neurological deficits.[130] The prevalence of methotrexate-induced leukoencephalopathy varies from 0% to 9% during therapy, and 16% to 69% after therapy.[131-133] Leukoencephalopathy can occur acutely or as a chronic toxic effect, especially if high-doses, multiple treatments or radiotherapy were also administered.[130] There is a greater risk of methotrexate-induced leukoencephalopathy in children under 5 years of age, and in patients who also receive cranial radiation therapy.[133]

Thus far, there are no validated biological predictors of methotrexate-induced leukoencephalopathy.[134] Several mechanisms have been proposed for the development of methotrexate-induced leukoencephalopathy including inhibition of CNS myelin turnover; inhibition of DHFR leading to deficiency of S-Adenosyl Methionine (SAM) and thus causing demyelination; inhibition of DHFR leading to folate and carbamin deficiencies, thus to hyperhomocystinaemia which is directly toxic to vascular endothelium; effects on CNS single-carbon metabolism causing demyelination; elevation of adenosine concentration in CSF which interferes with neurotransmitter synthesis; and impaired methionine metabolism influence methotrexate effects.[131,135] Genetic variants that disrupt methionine metabolism, and thus causing disturbances in the folate status, may enhance susceptibility to methotrexate-induced neurotoxicity. In a study of 68 patients with primary CNS lymphoma, the occurrence of methotrexate-induced white matter changes was significantly predicted by the presence of the low activity "Val/Val" / "T/T" genotype of *MTHFR* Ala222Val (677C>T, rs1801133), the "AA" genotype of *MTHFR* 1298A>C variant, and the "GG" genotype of transcobalamin 2 (*TCN2*) 776C>G variant, as well as male gender.[135] After analysis of a pediatric case report, Müller *et al*. hypothesized that methotrexate toxicity could be explained by the association of homozygosity of the *MTHFR* Ala222Val variant and a prolonged methotrexate exposure caused by the delayed methotrexate clearance.[136] In a case of severe, acute methotrexate-induced encephalopathy, homozygosity for a rare missense variant in methionine synthase (*MTR*) 2756A>G (D919G) was observed.[137]

ABC superfamily proteins *ABCB1*, *ABCC1-3*, and *ABCG2* are components of the cellular efflux system for methotrexate and may contribute to methotrexate toxicity.[138,139] In children with ALL, encephalopathy episodes were more frequent among children who have the *ABCB1* 3435 "TT" genotype than in the 3435 "CC/CT" group.[129] Finally, polymorphisms in *SLC19A1*, the methotrexate transporter, did not show an association with methotrexate-induced leukoencephalopathy.[128]

Methotrexate-induced Mucositis

Mucositis is a dose-limiting toxicity of methotrexate that is more frequent in young children.[140] Methotrexate mucositis is characterized by painful inflammation and ulceration of the mucous membranes lining the gastrointestinal tract that causes a significantly

reduced quality of life in 5-40% of patients receiving standard doses of methotrexate.[141-143] Mucositis increases the risk of potentially life-threatening systemic infection, as well as oral bleeding, abdominal pain, vomiting, diarrhoea, and dysphagia that limits the ability to take nutrition, hydration or medication by mouth.[142] The presence of any mucositis during a cycle of chemotherapy has been shown to significantly increase the frequency of infections and bleeding, and increase the likelihood of subsequent chemotherapy dose reductions, thereby reducing the efficacy of the cancer therapy.[141] In a study of 599 oncology patients, chemotherapy dose reductions occurred twice as frequently after patients developed mucositis.[140]

The mechanism of methotrexate-induced mucositis is not yet fully understood. The gut is especially sensitive to methotrexate because methotrexate blocks DNA synthesis causing cell cycle arrest and apoptosis in highly proliferative cells, such as the tumour cells and also cells in the gut.[144] There are several proposed mechanisms of methotrexate-mucositis, including alterations in glutathione metabolism, variations in gastrointestinal microflora,[145] and variable inflammatory responses by *TNF-a, IL-2, IL-6,* and *CRP*.[142,143] Genetic variants in these and probably other pro-inflammatory cytokines may play a role in methotrexate-toxicity and need further investigation.

The role of genetic factors involved in methotrexate metabolism and the risk of methotrexate mucositis is not well understood. As with methotrexate-induced leukoencephalopathy, the *MTHFR* gene has also been associated with methotrexate mucositis. Patients with a low activity "Val" allele of the *MTHFR* Ala222Val variant have a 20-36% higher "Oral Mucositis Index".[146] However, in some patient populations that have a higher frequency of this *MTHFR* variant, such as in Mexico (80% "Val" carriers vs. 42% in Caucasians), this variant was not associated with mucositis.[147] In this study, the authors postulated that the folate-rich diet of Mexican patients may have been an attenuating factor for methotrexate toxicity.

Glucocorticoid-induced Osteotoxicity

Glucocorticoids are frequently used for the treatment of ALL and lymphomas. The improved long-term survival pediatric cancer patients experience today has increased the risk of serious long-term effects on bone metabolism due to the adverse effects of glucocorticoids.[148] Glucocorticoid therapy is the most common cause of secondary iatrogenic osteoporosis and increases the risk of fractures, independent of age, sex and other known risk factors of fractures.[149] Glucocorticoid therapy longer than 3 months is associated with rapid bone loss, which varies with the dose and duration of the treatment.[150]

Children are more susceptible to glucocorticoid adverse effects than adults, and children are especially susceptible to adverse effects of glucocorticoids in the formation of growing bones.[151] However, the precise mechanisms of glucocorticoid osteotoxicity are unknown. Several genes involved in glucocorticoid metabolism could be promising targets for the identification of genetic variants that increase the risk of glucocorticoid-induced osteotoxicity. The corticosteroid binding globulin (*SERPINA6*) is responsible for glucocorticoid distribution. When glucocorticoids bind this protein, they are not available for metabolism.[152] The presence of polymorphisms in the *SERPINA6* gene may cause altered glucocorticoid binding and distribution, which could influence toxicity.

The development of glucocorticoid resistance has a significant impact for the risk of osteotoxicity because it frequently leads to increased glucocorticoid doses. The overexpression and several rare mutations in the glucocorticoid receptor gene (*NR3C1*) have been associated with glucocorticoid resistance.[153-157] It has been suggested that increased glucocorticoid receptor expression induces the expression of drug-metabolizing enzymes such as CYP3A4 and CYP2B6, possibly influencing toxic effects and glucocorticoid resistance experienced by patients.[158,159] The corticotrophin releasing factor receptor type 1 (*CRHR1*) is a major regulator of glucocorticoid synthesis. Polymorphisms in *CRHR1* are responsible for glucocorticoid-resistance in asthma patients, and increase the risk of osteotoxicity because of the increased doses required.[160]

The renal isoforms of *CYP27B1* and *CYP24A1* are responsible for the respective synthesis and

catabolism of 1,25-dihydroxyvitamin D3, the physiologically active form of vitamin D3. The expression of *CYP27B1* and *CYP24A1* are significantly altered by glucocorticoid administration and may contribute to the pathogenesis of glucocorticoid-induced osteoporosis by causing vitamin D deficiency, leading to reduced calcium absorption and reabsorption, and disrupted bone growth and bone remodelling. In mice, the administration of dexamethasone, a potent glucocorticoid, caused a 10-fold decreased expression of *CYP27B1*, and a 30-fold increased expression of *CYP24A1*, leading to reduced levels of active vitamin D3.[161-163] This disruption of renal vitamin D metabolism may contribute to the pathogenesis of glucocorticoid-induced osteoporosis but the implications of specific variants in these genes remain to be investigated.

Despite the number of genes associated with bone mass variation and osteoporosis, very little is known about specific polymorphisms contributing to glucocorticoid-induced toxicity in cancer patients. The significant consequences of bone fragility, bone fracture, and the risk of bone fracture in later life of paediatric cancer survivors warrants further research.

Future Perspectives

There is clearly a pressing need for additional research to address the significant problem of severe ADRs to cancer drugs that account for 22% of all pediatric oncology patient hospital admissions.[8] An obvious challenge in future case-control association studies in pediatric oncology is how to achieve sufficient statistical power to distinguish a real association from stochastic noise. The success of large-scale genome-wide screens with relatively small numbers of cases is limited to situations in which there is a small number of relatively common genetic risk factors, each with a large effect.[164] For severe ADRs, however, there is a growing number of examples where the genetic effect of the ADR is indeed large, such as carbamazepine-induced Stevens-Johnson syndrome,[165] abacavir-induced hypersensitivity,[166,167] statin-induced myopathy,[168] and gefitinib-induced diarrhoea.[169] The number of cases required to identify a highly significant association using a genome-wide scan in these examples is only 10 to 100 cases.[164] For example, a retrospective examination of a genome-wide scan of abacavir-induced hypersensitivity identified the chromosomal location of the causal *HLA-B**5701 variant among the 10 most significant SNPs when as few as 15 hypersensitivity reaction cases were analyzed.[164] Accurate and detailed clinical data are critical factors in the discovery of ADR susceptibility factors. Szoeke *et al.*[170] and the GAIN collaborative research group[171] recently highlighted the limitations of previous pharmacogenomic studies that lacked prospective case ascertainment and were deficient in detailed phenotypic and relevant clinical data to determine the role of genes versus other factors known to influence drug toxicity. Often missing were ancestry data, co-morbid conditions, medication doses, and concurrent medications, all of which are known to influence ADR risk. New pharmacogenomic studies, such as the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) are applying these principles to identify genetic factors of severe ADRs in children.[172-174] CPNDS employs experienced ADR surveillance clinicians that are trained to accurately recognize, document, and collect clinical data and biological samples from patients from more than 13 children's hospitals across the country, serving over 80% of the pediatric population. CPNDS also works closely with the C17 Research Network, which represents all 17 pediatric oncology treatment centres across Canada to investigate ADRs in pediatric oncology.

The safety of medications is an international concern. The rarity of some drug-induced severe ADRs and the absence of effective government ADR surveillance often make it difficult for any one research group to accrue enough patients to conduct effective genomic studies of ADRs. It is important that scientists, clinicians, industry, health care providers, and governments join forces and work together to understand the genetic basis of severe ADRs, especially in vulnerable populations such as pediatric oncology.

Clinical Implications

Removing medications from the market that have been shown to cause serious ADRs is not the solution, because this will leave seriously ill patients without therapy. Rather, the solution lies in identifying the mechanism for these ADRs, so that we can continue to use medications in patients for whom there is benefit, and better manage the risk in patients at high risk of ADRs.

The identification of genetic variants that contribute to serious ADRs is the first step to developing predictive diagnostic markers that will reduce the incidence of severe ADRs and improve treatment outcomes. A highly predictive diagnostic test to identify ADR susceptibility would benefit patients, families, and physicians by improving counselling and treatment options. In the future, patients at increased risk for these severe ADRs could (1) receive more aggressive monitoring for toxicity, or (2) be treated with alternative chemotherapy protocols, or (3) receive modified chemotherapy doses if there is evidence that this does not limit the medication's therapeutic effect in these patients, or (4) receive supplementary protective agents to proactively prevent the ADR. In the future, the identification of genetic variants that result in ADRs may also uncover a group of children who require chemotherapy dose intensification, which would potentially improve cure rates as well. Additional research is needed to address the significant problem of severe ADRs in children who are at greater risk of many serious adverse reactions and frequently develop more severe reactions with long term sequelae.

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