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Pharmacogenetic profiling of paediatric oncology patients: a single-centre experience

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Aim: As the results of pharmacogenetic studies are increasingly translated into clinical practice, the ultimate goal of personalising treatment for children with cancer seems achievable in the future. Our survey aimed to establish to what extent pharmacogenetics has already been utilised in everyday work.

Methods: A retrospective survey on pharmacogenetic testing in children treated for malignancies at the Department of Oncology and Haematology, Children's Hospital Zagreb, from 2021 to 2023 was carried out.

Results: Pharmacogenetic testing was performed in 17.2% of the 180 children (53.3% female, median age 7.0 years), the greatest number of tests obtained in 2023. Preemptive testing included thiopurine S-methyltransferase polymorphisms (in 94.4% of children with acute lymphoblastic leukaemia and 33.3% with eosinophilic granuloma) and methylenetetrahydrofolate reductase gene polymorphisms assaying (in 55.6% of acute lymphoblastic leukaemia and 23.1% of osteosarcoma patients). In 8 children, pharmacogenetic testing was made due to adverse events (25% lung and 75% liver injury, all grade 4), in the majority of cases presumably related to vincristine. Pharmacogenetic testing results were pathological in all reactively tested patients, requiring dose modification/chemotherapeutics omission in 87.5% of cases.

Conclusion: The number of pharmacogenetic assays performed due to high-grade adverse events in children with cancer has been continuously rising, steering otherwise standardised treatment towards a more individualised approach. Preemptive thiopurine Methyltransferase Polymorphism testing has been routinely done in almost all patients planned to receive thiopurines. However, more research is needed on drug-gene pairs in the field of paediatric oncology to minimise treatment-related toxicity and optimise treatment outcomes.

Keywords: PHARMACOGENETICS; PRECISION MEDICINE; MALIGNANCY; CHILDREN

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INTRODUCTION

Pharmacogenetics (PGx) studies variability in drug response determined by heredity. It includes predicting a patient's response to a particular therapy and susceptibility to toxicity and side effects (1). Therefore, PGx data can help select a specific drug and calculate individualised dosage for treating a particular condition. The main goal of PGx testing is to improve the safety and effectiveness of pharmacological therapy (2). Identifying genetic factors that influence the drug's absorption, metabolism, and action at the receptor level should enable individualised therapy. The results of a PGx test can reveal an individual's genetic predisposition to adverse drug reactions and differentiate those who respond to drugs from those who do not. It may also indicate the need for a different dosage of medication and, in some cases, the need to change to a completely different class of drugs. All this leads to the optimisation of therapy and better treatment efficiency to minimise toxicity, which is especially important when using cytostatics and other medications in paediatric haemato-oncology.

PGx testing can be reactive or preventive. Reactive testing occurs when a drug is prescribed paired with a known pharmacogene (i.e., a gene relevant to the clinical pharmacology of that particular compound). In contrast, preventive testing involves testing before prescribing the appropriate drug (3).

Drugs with narrow therapeutic ranges, drugs where drug concentration is monitored, drugs with variable efficacy and dose-limiting toxicity, and drugs with relatively common PGx side effects are of most significant interest for PGx trials. The results of PGx testing may not be directly helpful for every child or every drug. However, this does not mean it should not be available as part of routine care for children needing such testing. The limited availability of PGx testing and the absence of clear guidelines for testing in paediatrics represent an obstacle and impose the need to find better evidence of the usefulness of these tests in paediatric patients.

A particular problem is the extrapolation of the results of PGx tests from adults to paediatric patients and differences in the maturing of organ systems, enzymes, and transport functions concerning age, especially in the youngest age groups (4). Moreover, the test cost implies creating clear guidelines and criteria for selecting paediatric patients for PGx testing. On the other hand, adequate implementation of these tests enables the increased effectiveness of treatment and improved therapeutic outcomes, resulting in reduced morbidity and mortality. Specific PGx tests, such as thiopurine S-methyltransferase (TPMT) testing, are already routinely performed in paediatric haemato-oncology for patients scheduled for 6-mercaptopurine therapy (5).

In this retrospective study, we presented the results of PGx tests that are not part of specific protocols. Based on these results, therapeutic interventions were performed in paediatric patients suffering from malignant haematological diseases and malignant solid tumours.

METHODS

We conducted an observational, retrospective study on PGx testing in paediatric patients, aged 0-17, of both sexes, treated for haematologic malignancy and solid tumours at the Department of Oncology and Haematology in the Children's Hospital Zagreb, Croatia, from January 1st, 2021, to December 31st, 2023. Epidemiological and clinical data were taken from electronic medical records and included in appropriate tables. Clinical data included diagnosis, chemotherapy protocol, and adverse events of treatment, while epidemiological data comprised the age of patients at diagnosis, sex, and year of referral. Highlighted were the patients in whom PGx profiling was performed, either preemptively or reactively. Regarding preemptive testing in our study, we searched for specific pharmacogenes, the number of their pathological findings, and their impact on treatment. On the other hand, reactive testing in our research was performed after patients experienced adverse events during the treatment. A specific side effect of the treatment was recorded and evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE version 5). The pathological findings of a certain pharmacogene in reactive profiling and the need for consultation with a paediatric pharmacologist were noted. Furthermore, the necessity for omitting, delaying or modifying therapy was documented. Potentially new adverse events after cessation or modification of dosage were recorded. Descriptive statistics was carried out. The study was conducted according to the Declaration of Helsinki and approved by the Institutional Ethical Board.

RESULTS

Epidemiology

One hundred eighty patients participated in the study in a 3-year period, with a slight predominance of female patients (N = 96; 53.3%) and a mean age of 8.2 years (median 7.0 years, range 0.1-17 years). There were a total of 37 patients with haematologic malignancies (F = 21, 56.8%; M = 16, 43.2%) with a mean of 8.9 years (median 7.5 years, range 1-17 years) and 143 patients with solid tumours (F = 76, 53.1%; M = 67, 46.9), eight years of age in average. The distribution of patients according to diagnoses is shown in Figure 1.

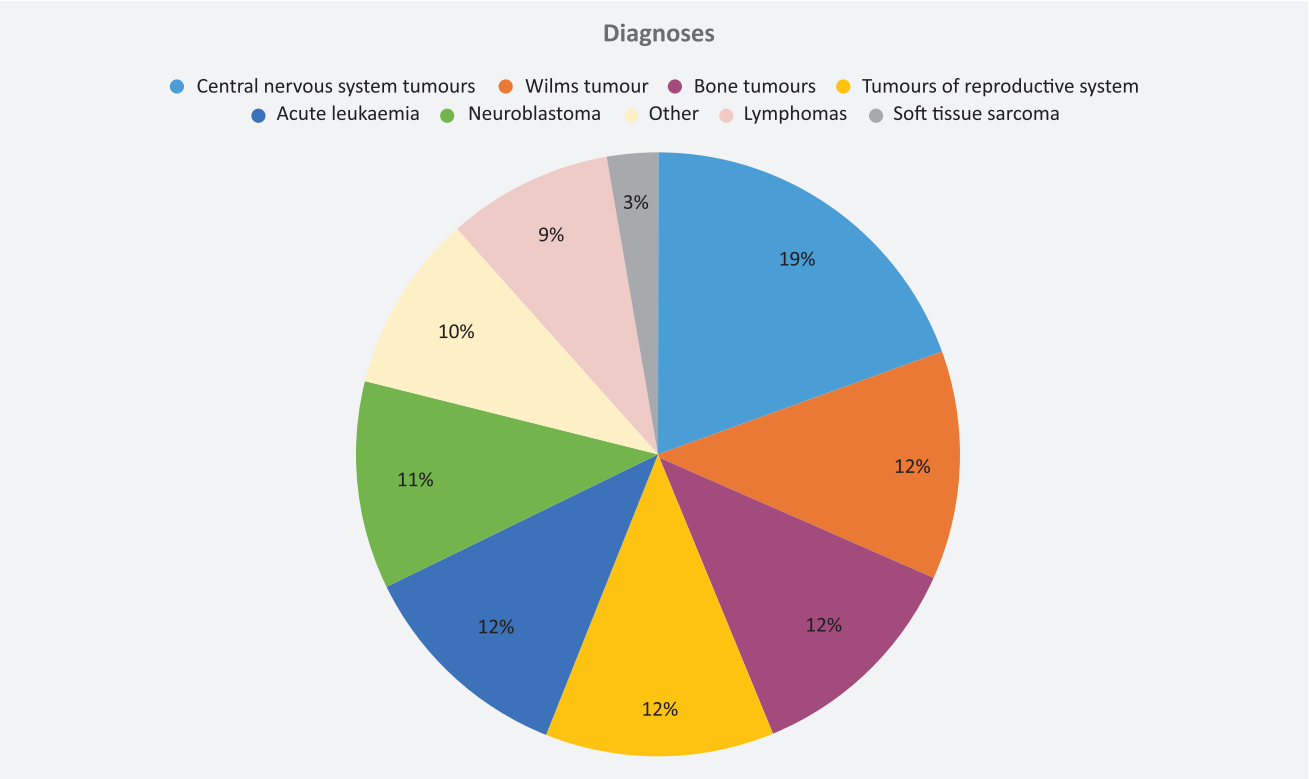

FIGURE 1. Distribution of patients according to diagnoses. In a three years, the majority of children were treated for tumours of the central nervous system (19%), followed by equal percentages of children (12%) treated for nephroblastoma, bone tumours, tumours of the reproductive system, and acute leukaemias. Other diagnoses are shown in the picture.

Overall pharmacogenomic profiling

A PGx profile was performed in 17.2% of patients (N = 31), preemptively in 12.8% (N = 23), and reactively in 4.4% (N = 8). Among all PGx profiles, 74.2% (N = 23) were carried out preemptively and 25.8% (N = 8) reactively. In two-thirds of patients with reactive PGx profiling, the assessment was performed at the beginning of treatment (induction or neoadjuvant chemotherapy regimen). Table 1 shows the characteristics of patients in whom the PGx profiling was performed reactively.

Preemptive pharmacogenomic profiling

C677T and A1298C polymorphisms of the MTHFR gene were performed in 55.6% (N = 10) of patients diagnosed with acute lymphoblastic leukaemia (ALL), while 90% of them (N = 9) had pathological findings. Three patients with abnormal MTHFR metabolism showed slower methotrexate elimination. On the other hand, TPMT*2,*3A, and *3C alleles of the TPMT gene were performed in almost every patient (N = 17, 94.4%) with ALL but were pathological in only one patient. Regardless of normal TPMT metabolism, four patients had treatment adverse events (transaminitis, hypoglycemia and leukopenia) during maintenance therapy and required dosage modification. In one patient whose intermediate metabolism of TPMT was recorded, dosage modification was not required, and the patient did not experience adverse events during treatment. MTHFR testing was done solely in three out of 13 osteosarcoma patients (23.1%), and pathological findings were found in two patients (N = 2). In only one out of three patients with eosinophilic granuloma, TPMT testing was performed, which showed normal TPMT metabolism.

Pharmacogenomic profiling by patient groups and year

In patients with haematologic malignancies, PGx was performed in 56.8% of patients (N = 21), preemptively in 48.6% (N = 18), and reactively in 8.1% (N = 3). In comparison, PGx testing was performed in only 7% of solid tumour patients (N = 10), with an identical number of reactive and preemptive models (N = 5, 3.5%). In 2021, PGx testing was carried out preemptively in 11.9% (N = 7/59), while none of the patients required reactive profiling. Next year, a total of eight PGx tests were performed, of which two (25%) were reactive. The year with the most significant number of PGx performed was 2023, preemptively in 14.7% (N = 10/68) and reactively in 8.8% (N = 6/68) of patients, respectively. Figures 2 and 3 show the number of patients by their group (haematologic malignancies or solid tumours), as well as the number and model of PGx profiling performed (reactive or preemptive).

TABLE 1. Characteristics of patients with reactively performed pharmacogenomic profiling.

Patient number		
1	Age (years)	3.5
	Sex	Female
	Diagnosis	Acute lymphoblastic leukaemia
	Protocol	ALL-IC BFM 2009
	Adverse event	Liver injury
	CTCAE (grade)	4
	PGx profile	ABCB1 (MDR1) c.1236C>T; ABCB1 (MDR1) c.3435C>T; ABCG2 c.421C>A; MRP2 (ABCC2) c.-24C>T; MRP2 (ABCC2) c.1249G>A; CYP3A4 *1B, *22; CYP3A5 *3; SLCO1B1 *5 (c.521T>C); TPMT *2, *3A, *3C; UGT1A1 *28; UGT2B7 -161C>T; PNPLA3 (I148M, rs738409, C>G)
	PGx (pathological findings)	ABCB1 and CYP3A5*3 intermediate activity; PNPLA3 heterozygous carrier
	Consultation of paediatric pharmacologists	No
	Incriminated drug	Vincristine
	Modification/omission of chemotherapy	Short-term delay of chemotherapy
	New adverse event related to repeated use of the incriminated drug	No
2	Age (years)	3.5
	Sex	Female
	Diagnosis	Acute lymphoblastic leukaemia
	Protocol	ALL-IC BFM 2009
	Adverse event	Liver injury
	CTCAE	4
	PGx profile	CYP2C9 *2, *3; CYP2C19 *2, *17; CYP3A4 *1B, *22; CYP3A5 *3; UGT1A1 *28; ABCG2 c.421C>A; ABCB1 (MDR1) c.2677G>T/A; ABCB1 (MDR1) c.3435C>T; MRP2 (ABCC2) c.-24C>T; MRP2 (ABCC2) c.1249G>A
	PGx (pathological findings)	CYP2C9*2,*3, CYP3A4*1B,*22, MRP2 (ABCC2) and MRP2 (ABCC2) intermediate metabolism; CYP2C19*2,*17 rapid metabolism; CYP3A5*3 no activity
	Consultation of paediatric pharmacologists	No
	Incriminated drug	Pegaspargase
	Modification/omission of chemotherapy	Chemotherapy delay for three weeks
	New adverse event related to repeated use of the incriminated drug	No
3	Age (years)	17
	Sex	Female
	Diagnosis	Hodgkin's lymphoma
	Protocol	EuroNet-PHL-C2
	Adverse event	Lung injury
	CTCAE	4
	PGx profile	CYP1A2 *1F (-163C>A, rs762551); CYP2D6 dupl, *3, *4, *6, *9, *10, *41; CYP3A4 *22; CYP3A5 *3; ABCB1 (MDR1) c.3435C>T; ABCG2 c.421C>A; SLCO1B1 *5 (c.521T>C)
	PGx (pathological findings)	CYP1A2*1F rapid activity; CYP2D6*3,*4,*6,*9,*10,*41 very rapid activity; CYP3A5*3 no activity; ABCB1 intermediate activity
	Consultation of paediatric pharmacologists	Yes
	Incriminated drug	Vincristine
	Modification/omission of chemotherapy	Omission of chemotherapy and conversion of vincristine to vinblastine
	New adverse event related to repeated use of the incriminated drug	No

▶

TABLE 1. Continued

Patient number		
4	Age (years)	6
	Sex	Male
	Diagnosis	Wilms tumour
	Protocol	Umbrella SIOP 2016
	Adverse event	Veno-occlusive disease
	CTCAE	4
	PGx profile	CYP3A4 *1B, *22; CYP3A5 *3; ABCB1 (MDR1) c.1236C>T; ABCB1 (MDR1) c.3435C>T; ABCG2 c.421C>A; MRP2 (ABCC2) c.-24C>T; MRP2 (ABCC2) c.1249G>A
	PGx (pathological findings)	CYP3A5*3, MRP2 (ABCC2) intermediate activity; ABCB1 low activity
	Consultation of paediatric pharmacologists	Yes
	Incriminated drug	Vincristine
	Modification/omission of chemotherapy	Lower doses of vincristine; omission of the first line of chemotherapy and conversion to carboplatin and etoposide
	New adverse event related to repeated use of the incriminated drug	Vincristine polyneuropathy
5	Age (years)	4
	Sex	Male
	Diagnosis	Wilms tumour
	Protocol	Umbrella SIOP 2016
	Adverse event	Veno-occlusive disease
	CTCAE	4
	PGx profile	CYP3A4 *1B, *22; CYP3A5 *3; ABCB1 (MDR1) c.3435C>T; ABCG2 c.421C>A; MRP2 (ABCC2) c.-24C>T ; MRP2 (ABCC2) c.1249G>A
	PGx (pathological findings)	CYP3A5*3 no activity
	Consultation of paediatric pharmacologists	No
	Incriminated drug	Actinomycin D
	Modification/omission of chemotherapy	Omission of actinomycin D for six weeks and afterwards modification to lower dosage
	New adverse event related to repeated use of the incriminated drug	No
6	Age (year)	2
	Sex	Female
	Diagnosis	Wilms tumour
	Protocol	Umbrella SIOP 2016
	Adverse event	Veno-occlusive disease
	CTCAE	4
	PGx profile	CYP3A4 *22; CYP3A5 *3; ABCB1 (MDR1) c.1236C>T; ABCB1 (MDR1) c.3435C>T; ABCG2 c.421C>A; MRP2 (ABCC2) c.-24C>T; MRP2 (ABCC2) c.1249G>A
	PGx (pathological findings)	CYP3A5*3 no activity
	Consultation of paediatric pharmacologists	Yes
	Incriminated drug	Vincristine
	Modification/omission of chemotherapy	Chemotherapy delay for six weeks and modification to lower dosage
	New adverse event related to repeated use of the incriminated drug	No

TABLE 1. Continued

Patient number		
7	Age (months)	4
	Sex	Female
	Diagnosis	Neuroblastoma
	Protocol	NB 2004 GPOH protocol
	Adverse event	Liver failure
	CTCAE	4
	PGx profile	TPMT *2, *3A, *3C; ABCB1 (MDR1) c.3435C>T; ABCG2 c.421C>A; MRP2 (ABCC2) c.-24C>T; MRP2 (ABCC2) c.1249G>A; SLCO1B1 *5 (c.521T>C)
	PGx (pathological findings)	TPMT**2, *3A, *3C, MRP2 (ABCC2) intermediate activity; ABCB1 (MDR1) no activity
	Consultation of paediatric pharmacologists	No
	Incriminated drug	Vincristine
	Modification/omission of chemotherapy	Omission of chemotherapy
	New adverse event related to repeated use of the incriminated drug	No
8	Age (years)	2
	Sex	Male
	Diagnosis	Pleuropulmonary blastoma type II
	Protocol	COG protocol (for Ewing sarcoma)
	Adverse event	Acute respiratory distress syndrome
	CTCAE	4
	PGx profile	CYP2C9 *2, *3; CYP2C19 *2, *17; CYP3A4 *1B, *22; CYP3A5 *3; ABCB1 (MDR1) c.1236C>T; ABCB1 (MDR1) c.3435C>T; ABCG2 c.421C>A; MRP2 (ABCC2) c.-24C>T; MRP2 (ABCC2) c.1249G>A; SLCO1B1 *5 (c.521T>C)
	PGx (pathological findings)	CYP2C19*2, *17 rapid metabolism; CYP3A5*3 no activity; ABCB1 (MDR1), ABCG2, SLCO1B1*5 low activity; MRP2 (ABCC2) intermediate activity
	Consultation of paediatric pharmacologists	Yes
	Incriminated drug	Vincristine
	Modification/omission of chemotherapy	Omission of chemotherapy
	New adverse event related to repeated use of the incriminated drug	No

DISCUSSION

Relatively favourable overall outcomes in children and adolescents with malignant diseases over the past few decades have been mainly attributed to risk-adapted chemotherapy protocols and supportive therapy improvements. However, as molecular testing has increasingly been utilised in adults with cancer as part of precision medicine trials, efforts have been made to integrate genome sequencing into standard clinical practice in paediatric oncology (6).

Namely, PGx offers an opportunity to minimise toxicity and optimise the effectiveness of chemotherapy regimens since the diversity in inter-individual drug response can be explained to a great extent by genetic variations and epigenetic signatures acquired during the process of oncogenesis, affecting drug pharmacodynamics and pharmacokinetics (7). Nevertheless, specific medicine response profiles result from the complicated interaction between pharmacogenes and the environment and need to be interpreted with caution in the context of this complex interplay (8).

Our survey results indicate the rising trend of PGx testing over the three-year period. The extent of the preemptive PGx approach, predominantly based on TPMT polymorphism assays, has remained relatively the same in time and has become the standard part of diagnostic algorithms in children with ALL. The reactive PGx approach, also with direct implications regarding further chemotherapy administration, has been applied more frequently, mostly in children with solid tumours and those who have experienced high-grade AEs, predominantly liver injury.

The decision on PGx testing applying a preemptive approach was made solely by the paediatric oncologist. It was based principally on the Clinical Pharmacogenetics Imple-

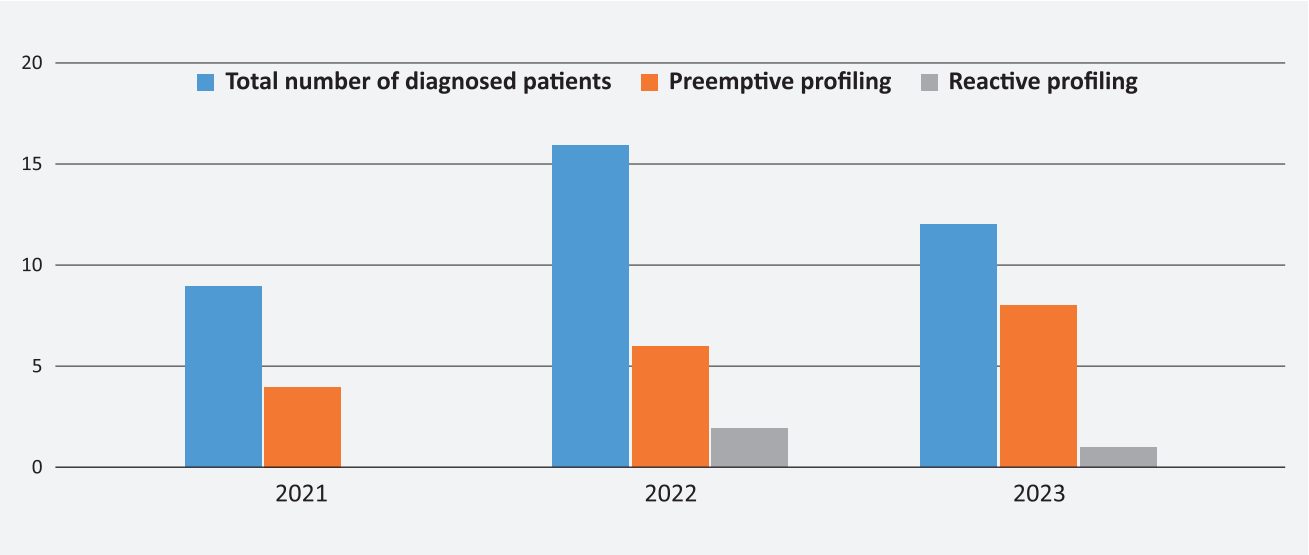

FIGURE 2. Pharmacogenomic profiling in paediatric patients with haematologic malignancies. In the group of patients diagnosed with leukaemia or lymphoma (N = 37), the most significant number of preemptive pharmacogenomic profiling was performed in 2023 (N = 8), while the largest proportion of reactively performed tests in this group of patients (N = 2) were conducted in 2022.

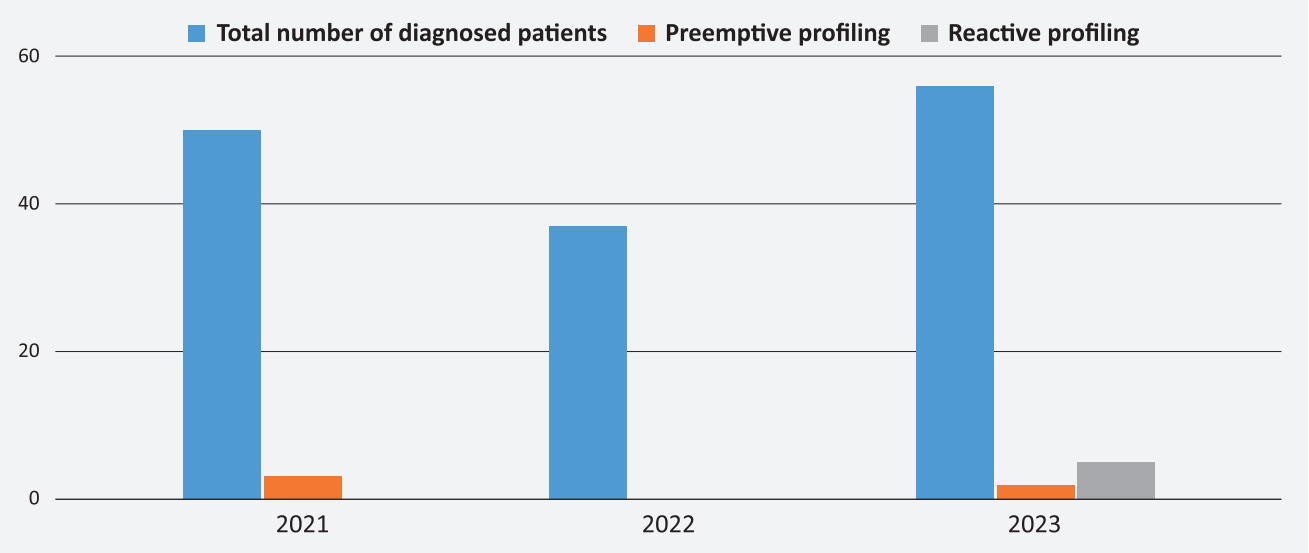

FIGURE 3. Pharmacogenomic profiling in paediatric patients with solid tumours. The year with the greatest number of patients diagnosed with solid tumour was 2023 (N = 56), when the greatest number of reactive pharmacogenetic tests in this group of patients were performed (N = 5).

mentation Consortium guideline (CPIC) (9), barely influenced by the physician's personal attitudes and practice. Conversely, which pharmacogenes should be tested in cases of severe AEs was discussed thoroughly among the attending physician and the pharmacogenetics laboratory personnel, taking into account recently administered cytostatics and the nature of the side-effect. Supportive therapeutics were not considered possible causative agents. Therefore, pharmacogenes responsible for their metabolism were not purposely included in the PGx panel.

TPMT polymorphism testing has been available in Croatia for almost twenty years. Although not a mandatory part of the initial diagnostics according to the ALL-IC BFM 2009 study, a protocol used to treat children with ALL in our country, it was routinely performed in almost all our ALL patients. Since CPIC guidelines from 2018 offer straightforward instructions on thiopurine dose adjustments, more contemporary European protocols, such as ALLtogether and ALL-IC BFM 2022, have included TPMT polymorphism assaying in baseline work-up algorithms. Myelosuppression and mild to moderate liver toxicity were still occasionally encountered during the maintenance therapy in our patients with adequate thiopurine metabolism according to the TPMT genotypes; the need to introduce additional pharmacogenetic investigations, such as NUDT15 in our national pharmacogenetics panel should possibly be ad-

dressed. Namely, although pathological alleles of NUDT15 genes are commonly discovered in people of Asian or Hispanic origin, they could also be responsible for thiopurine toxicity in patients of European descent (9, 10).

MTHFR C677T polymorphism was associated with methotrexate (MTX) toxicity, mostly haematological and gastrointestinal, in adults with haematological malignancies (11), which was also recently confirmed in children with ALL receiving high-dose MTX (12). In half of our ALL patients, MTHFR polymorphism assays were performed, often as a part of a thrombophilia panel. Although in the vast majority of cases, findings were pathological, the results of our survey failed to establish the link to MTX serum elimination. At the same time, the association with hepatic and haematological toxicity was not studied. The current CPIC level MTHFR-MTX pharmacogene-drug pair carries level C, so no prescribing actions are recommended (13).

Over the last decades, vincristine (VCR) has been implemented in most of the paediatric solid tumour and haematologic malignancies protocols, its main AE manifesting as pain, tingling sensation and loss of muscle strength, or in general, sensory, motor and autonomic symptoms of well-studied vincristine-induced peripheral neuropathy (VIPN) (14, 15). Polyneuropathy related to VCR use might be due, among many others, to polymorphisms in ACTG1, CAPG, ABCB1 and especially CEP72 genes (16, 17, 18). At the same time, a recent meta-analysis failed to provide enough evidence on the previously established causative link between CYP3A5 expression and VIPN (14). Apart from the peripheral and central nervous system toxicity, the most commonly described VCR side effects, seldomly encountered toxicities include gastrointestinal symptoms, cardiovascular abnormalities and hepatic disorders (15). Based on the Food and Drugs Administration (FDA) AEs reporting system, VCR has been discerned as the third most common medication known to cause liver injury in children, with paracetamol and MTX placed first and second, respectively (19).

In all eight of our patients, VCR was an incriminated drug, causing hepatic injury in two-thirds of cases, half meeting the criteria for veno-occlusive disease (VOD), necessitating defibrotide administration that resulted in complete recovery. VOD or sinusoidal obstruction syndrome (SOS) occurs in one-third of children undergoing allogeneic haematopoietic stem cell transplant (alloHSCT), especially in infants and patients with pre-existing liver disease. It presents within three weeks from transplant with unexplained weight gain, ascites, jaundice and hepatomegaly, as well as thrombocytopenia (20). Along with alkylating agents used in preparative regimens, SOS is associated with actinomycin D and VCR (15, 20), cytostatics that are the mainstay of treatment in nephroblastoma. All three of our patients with Wilms tumour that experienced SOS showed intermediate or no CYP3A5*3 activity, guiding the attending physician's decision towards dosage modification or chemotherapy regimen substitution.

Drug-induced acute lung injury (DALI) typically develops within three days of drug exposure (21); therefore, in one adolescent patient, sudden onset of respiratory symptoms with interstitial lung involvement was also attributed to VCR administration. Since pulmotoxicity in a small proportion of cases occurs sub-acutely, even four weeks after the medicine application, a potentially harmful agent in this patient might have been etoposide, also reported to cause DALI (21). Nevertheless, due to the CYP3A5*3 result showing no activity, DALI was ascribed to VCR, as was in a preschooler with rare pleuropulmonary blastoma, examples of PGx testing being a valuable tool for a clinical practitioner regarding therapeutic decision making.

As CPIC guidelines offer straightforward instructions on dose modifications related to TPMT polymorphisms assay results, paediatric oncologists at our centre often feel confident interpreting PGx findings and seldom seek additional advice regarding thiopurine therapy dosage in children with ALL. However, in cases of severe drug toxicity, as in half of our patients in whom the reactive PGx approach was applied, counsel from the institutional clinical pharmacologist was requested. Namely, as literature data on pharmacogene-drug relations other than TPMT-thiopurines is not as unambiguous, healthcare providers feel uncomfortable interpreting and applying PGx results, as reported by Mowbray et al (22).

Nevertheless, according to a recent study from China, 60% of clinical pharmacists feel insecure about providing PGx testing and accompanying services, and about 90% require a thorough literature search to provide answers for clinical practitioners (23). However, pharmacists have played a pivotal role in the implementation of pharmacogenomics and pharmacogenetics into everyday practice and remain crucial parts of the PGx chain, continuously affirming, evaluating and consulting (24). Nonetheless, a report from the Working Group of the Royal College of Physicians and British Pharmacological Society clearly stated the necessity of a collective and multidisciplinary approach in pharmacogenetics clinical implementation. It highlighted the joint involvement of pharmacists, doctors and other healthcare providers, such as biochemists and clinical geneticists, engineers and informatics experts, and patients (25).

The authors are aware of the possible limitations of this survey. Retrospective, single-centre design offers an inferior level of evidence and lacks scientific vigour. Additionally, attribut-

ing causality is an unavoidable obstacle in drug-related studies. However, that was not the goal of our investigation. Namely, this is the first study to explore PGx testing implementation in clinical routines in paediatrics in Croatia and the demanding and complex field of paediatric oncology.

CONCLUSION

Although pharmacogenomics of chemotherapeutics is a challenging yet steadily evolving field in paediatric oncology, PGx testing is increasingly more often integrated into contemporary clinical diagnostic-therapeutic approaches. While, according to the international guidelines, TPMT polymorphism testing has routinely been done in children with ALL receiving thiopurines as part of the initial work-up, recommendations regarding other pharmacogene-drug pairs investigations still lack sufficient evidence to be implemented in everyday clinical practice. Nevertheless, in cases of high-grade toxicities, PGx presents a valuable tool that provides possible side effects explanations as well as guidance for further management.

Abbreviations:

ALL – Acute lymphoblastic leukaemia
AEs – Adverse events
AlloHSCT – Allogeneic haematopoietic stem cell transplant
CPIC – Clinical Pharmacogenetics Implementation Consortium guideline
DALI – Drug-induced acute lung injury
FDA – Food and Drugs Administration
MTX – Methotrexate
MTHFR – Methylenetetrahydrofolate reductase
PGx – Pharmacogenetics
TPMT – Thiopurine S-methyltransferase
VCR – Vincristine
VIPIN – Vincristine-induced peripheral neuropathy
VOD – Veno-occlusive disease
SOS – Sinusoidal obstruction syndrome

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SAŽETAK

Farmakogenetsko profiliranje pedijatrijskih onkoloških bolesnika: iskustvo jednog centra

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Cilj: Kako se rezultati farmakogenetskih studija sve više prevode u kliničku praksu, krajnji cilj, personalizacija liječenja djece s rakom, čini se dostižnim u bliskoj budućnosti. Cilj našeg istraživanja bio je utvrditi u kojoj se mjeri farmakogenetika već koristi u svakodnevnom radu.

Metode: Provedeno je retrospektivno istraživanje o farmakogenetskom testiranju u djece liječene zbog zloćudnih bolesti u Zavodu za onkologiju i hematologiju Klinike za dječje bolesti Zagreb od 2021. do 2023. godine.

Rezultati: Farmakogenetsko testiranje je učinjeno u 17,2% od ukupno 180 djece (53,3% ženskog spola, medijan dobi 7,0 godina), najveći broj testiranja učinjen je 2023. Preemptivno testiranje uključivalo je polimorfizme gena tiopurinmetiltransferaze (u 94,4% djece s akutnom limfoblastičnom leukemijom) i 33,3% s eozinofilnim granulomom) i ispitivanje polimorfizama gena metilentetrahidrofolat-reduktaze (u 55,6% pacijenata s akutnom limfoblastičnom leukemijom i 23,1% pacijenata s osteosarkomom). U 8 djece farmakogenetsko testiranje je učinjeno zbog nuspojava lijeka (25% plućna i 75% hepatotoksičnost, sve 4. stupnja), u većini slučajeva vjerojatno povezanih s vinkristinom. Rezultati farmakogenetskog testiranja bili su patološki u svih reaktivno testiranih bolesnika, zahtijevajući prilagodbu doze/izostavljanje kemoterapije u 87,5% slučajeva.

Zaključak: Broj farmakogenetskih testova koji se izvode zbog toksičnosti visokog stupnja kod djece oboljele od malignih bolesti kontinuirano raste, usmjeravajući inače standardizirano liječenje prema individualiziranijem pristupu. Preemptivno testiranje polimorfizma gena tiopurinmetiltransferaze rutinski se provodi u gotovo svih pacijenata u kojih je planirana primjena tiopurina. Međutim, potrebno je više istraživanja o parovima lijek-gen u području pedijatrijske onkologije kako bi se smanjila toksičnost povezana s liječenjem i optimizirali ishodi liječenja.

Ključne riječi: FARMAKOGENETIKA; PERSONALIZIRANA MEDICINA; MALIGNA OBOLJENJA; DJECA