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Review Paper

NUDT15 as a Predictive Biomarker for 6-Mercaptopurine-Induced Toxicity in Indian Pediatric Patients with Acute Lymphoblastic Leukemia: A Systematic Review

Renupriya J*, Mohamed Adil N, Suriya P, Jayalakshmi Venugopal

Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore-641048.

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is the most common form of haematological cancer in children, accounting for about a quarter of all childhood cancer cases worldwide. While there have been major advances in risk adapted chemotherapy and a significant improvement in the overall survival rate (now approximately 85%), treatment related toxicities remain to be a risk for therapeutic success. Maintenance chemotherapy, usually a combination of weekly injections of methotrexate and daily oral 6-mercaptopurine (6-MP), is very useful to help prevent a relapse. It has been noted, however, that there is substantial interindividual variation in 6-MP metabolism that can lead to hepatotoxicity and, more importantly, to a wide range of severe hematological toxicities including leukopenia, neutropenia, thrombocytopenia, pancytopenia, and anemia which require discontinuation and dose reduction of the drug. One of the main factors influencing this variability has been identified is pharmacogenetic differences. One of the pharmacogenetic markers identified has been the Nudix Hydrolase 15 (NUDT15) which has been the subject of much discussion because of its significant association with thiopurine intolerance, particularly in Asian patients. Variations that affect the function of the enzyme, especially NUDT15 c.415C>T (p.Arg139Cys), slow down the breakdown of active thioguanine metabolites, causing an increase in DNA incorporation and serious myelosuppression, even at standard therapeutic doses. A number of studies have been performed in India which have demonstrated that SNPs of NUDT15 gene are highly correlated with thiopurine-related toxicity and less tolerance to 6-MP in children with ALL. Therefore, the use of genotype guided dose optimization is gaining recognition as an effective approach to limit the occurrence of adverse medication reactions without compromising therapeutic effectiveness. This review summarises the information available on the role of NUDT15 polymorphisms as

***Corresponding Author:** Renupriya J
Address: *Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore-641048*
Email ✉: renujagadeesh20@gmail.com

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prognostic biomarkers for 6-MP induced toxicity in Indian paediatric ALL patients. The study also discusses the existing pharmacogenetic guidelines, evidence from Indian and international studies, molecular mechanisms of thiopurine metabolism and future prospects of precision medicine in paediatric oncology

INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common type of cancer in children, is about 25–30% of all childhood cancers worldwide. It is characterized by the unchecked proliferation of inadequate precursor lymphoid cells in the bone marrow and it results in disturbed normal hematopoiesis and immunological dysfunction. Modern chemotherapy, risk assessment, and supportive care have improved the likelihood of long-term survival to now better than 85%. These have all been important improvements, yet treatment-related toxicities remain an important issue that often requires dose adjustments, interruption of therapy, and increased morbidity.

An important aspect of the treatment of ALL is what is called maintenance chemotherapy, which is used to help kill any remaining leukemic cells and prevent the ALL from coming back. The maintenance therapy is based on weekly methotrexate and daily oral 6-mercaptopurine (6-MP). Despite its high efficacy 6-MP has high inter-individual variation of toxicity and metabolism. Many patients tolerate normal doses without serious side effects, such as leukopenia, neutropenia, thrombocytopenia, pancytopenia, anemia or hepatotoxicity, highlighting the need for individualized treatment approaches.

Many enzymes, such as thiopurine S-methyltransferase (TPMT) and Nudix Hydrolase 15 (NUDT15), control the metabolism of 6-MP. TPMT polymorphisms were previously believed to be the primary reason for thiopurine intolerance, but the prevalence of severe toxicity among those who have them was not easily accounted for by the low frequency of these polymorphisms in the Asian population. Subsequent studies revealed the importance of NUDT15 as a pharmacogenetic marker for thiopurine intolerance, particularly in Asians.

Reduced-function polymorphisms, especially NUDT15 c.415C>T (p. Arg139Cys), decrease the metabolism of active thioguanine metabolites and cause increased DNA incorporation, resulting in severe myelosuppression in patients even at standard doses of 6-MP.

The clinical relevance of NUDT15 is particularly important in India where several studies have revealed a strong association between the variations in NUDT15 and 6MP-toxic toxicity in children with ALL. Pharmacogenetic testing allows for early identification of individuals that are genetically vulnerable and enables genotype-guided dose optimization, which reduces the toxicity of treatment while maintaining its effectiveness. Therefore, this review aims to emphasize the possible role of the NUDT15 polymorphisms in precision medicine and tailored therapy and also summarize the existing evidence of their role in predicting the 6-mercaptopurine-induced toxicity in Indian children with ALL.

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is a malignant disease of the lymphoid progenitor cells characterized by uncontrolled multiplication and accumulation of immature lymphocytes in the bone marrow, peripheral blood and extramedullary tissues. It's the most prevalent cancer in children, accounting for approximately 25% of all childhood cancers around the world, and almost 80% of all childhood leukemias. However, males are a little more likely to experience the most common occurrence, which takes place between the ages of two and five. The precise etiology of leukemogenesis is not yet known, but it is believed to be a complex process that involves inherited genetic susceptibility, abnormalities in

chromosomes, environmental exposures and acquired somatic mutations that disrupt normal lymphoid development and cell death.

According to the World Health Organization (WHO), there are two types of ALL: B-cell precursor acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL), with B-ALL representing approximately 80-85% of all cases of ALL in children. Several common cytogenetic abnormalities, including ETV6-RUNX1 fusion, hyperdiploidy, BCR-ABL1 translocation and KMT2A rearrangements, exert a significant influence on the treatment and prognosis of the disease. Fever, exhaustion, pallor, recurrent infections, bleeding tendencies, bone pain, hepatosplenomegaly, lymphadenopathy, and involvement of the central nervous system are typical clinical symptoms. The diagnosis is made by peripheral blood testing, bone marrow aspiration, immunophenotyping, cytogenetic analysis and molecular diagnostic techniques.

Treatment for paediatric ALL has undergone many changes over the last few decades and in wealthy nations over 85% of children now survive. Four consecutive steps make up modern treatment protocols: induction, consolidation (intensification), interim maintenance, and protracted maintenance therapy. One of these phases is critical to reducing the number of remaining cells of the disease, and to preventing a second attack – maintenance therapy. This long-term treatment period usually runs for 2 to 3 years, and is primarily made up of 6-mercaptopurine given as an oral pill daily and methotrexate given weekly. It is important to ensure that the drug is optimally maintained and that any toxicities of the drug treatment are minimised. Hence, dose modification of 6-mercaptopurine is one of the most important aspects of current ALL management in children.

6-MP MAINTENANCE THERAPY

For almost fifty years, 6-mercaptopurine (6-MP), a synthetic thiopurine analogue, has been the mainstay of maintenance chemotherapy for juvenile acute lymphoblastic leukemia. Because of its strong antileukemic action and good therapeutic efficacy when given over extended periods of time, 6-MP, which was first introduced in the 1950s, continues to play a critical role in maintaining long-term remission. The daily oral dose of 6-MP combined with weekly methotrexate greatly reduces recurrence rates by blocking the growth of leukemic cells resistant to induction and consolidation therapy.

Following oral administration, 6-MP is metabolized in a complex fashion within cells, and includes multiple competing metabolic pathways. Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) transforms the medication into thioinosine monophosphate, which then goes through a number of enzymatic changes to produce active thioguanine nucleotides (TGNs).

The result of these compounds incorporation into nucleic acids is inhibition of nucleic acid synthesis, disruption of DNA replication and induction of apoptosis, and suppression of leukemic cell proliferation. Further, 6-MP undergoes alternate metabolic pathways through xanthine oxidase and thiopurine S-methyltransferase (TPMT) to regulate the intracellular levels of 6-MP and reduce the risk of over-accumulation of the drug and its attendant toxicity.

However, despite its high therapeutic effectiveness in preventing recurrence, 6-MP has a relatively narrow therapeutic window to its toxic effects which creates a significant clinical challenge. There are wide differences in the metabolism of a drug among individuals, and as a result, there are significant variations in the toxicity and therapeutic response that can be seen when the

same doses are given. Some patients may suffer from severe hematological toxicity in the first weeks of treatment while others may be able to use conventional doses while on maintenance therapy. Severe neutropenia, leukopenia, thrombocytopenia, pancytopenia, anemia, recurrent infections, febrile neutropenia, mucositis, gastrointestinal intolerance, hepatotoxicity are all indications for dose interruption or substantial decrease in dose. Maintenance chemotherapy may be compromised by frequent treatment disruptions, which could raise the chance of disease relapse and have a detrimental impact on long-term survival.

Initially, differences in the TPMP gene seemed to be responsible for the different levels of thiopurine toxicity. However, because there were relatively few TPMT mutations found in Asian cultures, the possibility of other genetic causes of thiopurine intolerance arose. Due to this result, NUDT15 was found to be a significant pharmacogenetic determinant of 6-MP toxicity, especially in Asian children with ALL. This genetic correlation has transformed the dosage of thiopurines and established pharmacogenetic dosing as an integral component of cancer personalized therapy.

NUDT15 GENE AND ITS ROLE IN THIOPURINE METABOLISM

A member of the Nudix hydrolase family that hydrolyzes oxidized nucleotides and preserves intracellular nucleotide homeostasis is encoded by the Nudix Hydrolase 15 (NUDT15) gene, which is found on chromosome 13q14.2. NUDT15 is a protective enzyme which converts active thioguanine triphosphate (TGTP) and thiodeoxyguanosine triphosphate (TdGTP) to their inactive monophosphate forms during thiopurine metabolism. This hydrolytic process protects rapidly dividing hematopoietic cells from severe DNA damage and apoptosis by preventing DNA incorporation of excessive amounts of harmful thioguanine metabolites during cellular replication.

The genetic changes in the NUDT15 gene that significantly reduce enzyme activity lead to accumulation of active thioguanine nucleotides inside the cell. The missense mutation c.415C>T (p.Arg139Cys) has continuously shown the highest correlation with thiopurine intolerance among the several variants found.

Such an amino acid substitution destabilizes the NUDT15 protein, substantially reduces its catalytic ability and increases the level of toxic metabolites in the cells. Thus, even when patients receive the usual dose of 6-MP, they experience severe myelosuppression when heterozygous or homozygous for the mutants.

Ethnic diversity of NUDT15 polymorphisms are noted. The reduced function variants are relatively uncommon in European, African and South American populations but are much more prevalent in East Asian, South-East Asian and Indian populations. This ethnic distribution is important because it would account for the majority of the thiopurine toxicities observed in Asian patients that are not due to TPMT polymorphisms, and because it underscores the importance of conducting ethnic-specific pharmacogenetic screening before initiating maintenance chemotherapy.

MECHANISM OF NUDT15-MEDIATED 6-MERCAPTOPURINE TOXICITY

NUDT15 acts as a "brake" by preventing the active DNA-inserting metabolites of thiopurine (TGTP, TdGTP) from causing damage, acting as a protective mechanism before they can harm DNA. Loss-of-function variants (especially c.415C>T) reduce this braking effect. This leads to TGNs being accumulated and too well integrated into DNA, leading to replication stress and apoptosis in bone marrow precursor cells. Catherine presented an acute or life-threatening myelosuppression

clinically. Patients who are heterozygous variants have a reduced, but clinically meaningful, degree of tolerance, and homozygous variants have reduced tolerance to a degree that demands substantial dose reduction. Importantly, NUDT15 deficiency is the predominant genetic cause of thiopurine intolerance in East, Southeast and South Asian people, whereas TPMT insufficiency is not common in these patients; therefore it is very important to genotype NUDT15 in Indian patients.

EVIDENCE FROM INDIAN STUDIES

The same is concluded by some Indian studies too where NUDT15 c.415C>T is significantly associated with early leukopenia, neutropenia, thrombocytopenia, pancytopenia and interruption in treatment of pediatric ALL. However, its prevalence in Indian children is greater than that of TPMT variants – making NUDT15 the more relevant marker in the local context. It has been shown that dose reduction according to genotype does not affect the control of leukemia but significantly reduces the doses for heterozygotes and much more for homozygotes to reduce the risk of severe (Grade 3/4) toxicity. Further, the option of pre-treatment genotyping is touted as an effective way of reducing costs, as hospitalisation, transfusion and antibiotic use due to toxicity are costly. The study warns that the evidence is consistent in India, but it comes from small-scale, single-center studies, and as such is less widely applicable to the nation at large.

COMPARISON WITH INTERNATIONAL EVIDENCE

Although the European and North American studies and data still indicate TPMT as the most important toxicity predictor in Asian populations, the Japanese, Korean, Chinese, Thai, Singaporean and Taiwanese studies all support NUDT15 (not TPMT). This ethnic heterogeneity is a refutation to the idea of a one size fits all pharmacogenetics approach. Worldwide, genotype-directed dosing is proven to remain effective, reduce hospitalization, cost and febrile neutropenia

CLINICAL IMPLICATIONS AND CPIC RECOMMENDATIONS

CPIC recommends pre-treatment genotyping for TPMT and NUDT15. The normal metabolizers will receive the usual starting doses, intermediate metabolizers will receive lower doses, but with careful dose titration, and poor metabolizers will receive significantly lower doses, and fewer doses. This could be a first step towards the precision oncology approach, especially in settings where NUDT15 polymorphisms are common, moving from reactive (tweak dosage after toxicity appears) to proactive, personalized dosing.

CHALLENGES AND LIMITATIONS

As a reliable biomarker to predict the toxicity of 6-mercaptopurine, it is not widely used in the clinic. The results of the majority of Indian studies have limited generalizability, due to small sample sizes, single-center designs, and inconsistent treatment methods. The high cost and limited availability of pharmacogenetic testing, limited molecular diagnostic facilities, and lack of clinician awareness are also contributing factors to the low level of adoption of genotype-guided therapy. Due to the fact that several genetic and non-descendant factors affect thiopurine toxicity in children with ALL, more multicenter studies are required to develop a standardized pharmacogenetic guidelines for children with ALL from India.

FUTURE PRESPECTIVE

Large multicenter prospective studies should be the main focus of future research in order to confirm the clinical usefulness of NUDT15-guided dosage in Indian children with ALL.

Enhancing the safety of medications and reducing adverse effects due to toxicity can be done through increasing availability of reasonably priced pharmacogenetic testing and incorporating NUDT15 screening into routine clinical care. The complete pharmacogenomic approach is expected to be possible, with the help of the advances in AI, precision medicine, and next generation sequencing, to enable tailored thiopurine therapy and improve long-term patient outcomes.

CONCLUSION

NUDT15 is an important pharmacogenetic biomarker that is critical for predicting 6-mercaptopurine-induced toxicity, particularly in Asian patients with ALL. Identification of NUDT15 polymorphisms prior to treatment enables dosages to be adjusted to reduce high levels of haematological toxicity without compromising efficacy. While the practical application of pharmacogenetic testing is still challenging, increasing research efforts and wider use of genotype-directed treatment could improve patient safety, optimize treatment outcomes, and advance precision medicine in pediatric oncology

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