A Comparative Study of Different Pharmacogenomic Treatments for Acute Lymphocytic Leukemia (ALL)

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Introduction

Acute Lymphocytic Leukemia (ALL) is the most prevalent childhood cancer today. According to the World Health Organization and *Frontiers in Public Health*, it accounts for approximately 285,095 of 400,000 cases (71%) of cancer development in children aged 0-19 globally per year. In Canada, The five-year survival rate is 51%, and ALL patients have a significantly lower quality of life, as a result of adverse drug reactions (ADRs) to their treatment (Canada Cancer Society, n.d., pg. 1).

Primarily, current treatment involves long-term chemotherapy to induce remission in three phases: induction, consolidation, and maintenance. Chemotherapy treats ALL by killing rapidly-dividing, abnormal lymphocytes known as lymphoblasts in the bone marrow (Mayo Clinic Staff, 2024, pg. 1). Lymphoblasts are the precursor cells of lymphocytes, a type of white blood cell. Because those cells are not differentiated, they can evade cell cycle check points and grow uncontrollably. In ALL, they spread by rapidly replicating themselves through the evasion of check points during DNA replication. To prevent the spread of lymphoblasts, ALL treatments target to disrupt the replication, inducing the cells' programmed death, apoptosis.

Chemotherapy treatment poses a high risk of patients experiencing adverse drug reactions. Such reactions add to the disease burden of the therapy, and compromise the patient's quality of life. In a study among 123 pediatric cancer patients, 87% of pediatric patients experienced at least one ADR (Mutagonda, 2022, pg. 1). ADRs are caused by an adverse reaction of the drug with a particular genetic variant in a patient's genetic profile. This means that when the drug comes into contact with certain proteins in the patient's body, ADRs occur because the variant of the gene that encodes that protein is simply incompatible with the drug being used (Mutagonda, 2022, pg. 1). No chemotherapy treatment is universally compatible, and to find the right one for a patient, their genetic profile must be taken into consideration, as some gene variants react adversely to certain drugs.

To overcome this issue, pharmacogenomic (PGx) treatment methods are used. PGx treatments refer to the interaction between a patient's genetic predisposition to their therapeutic drug responses. In such treatments, genetic variants that may result in ADRs with particular chemotherapy drugs are located prior to induction via genetic testing. This is to ensure compatibility between the patient's genetic profile and the chemotherapy drug being used.

Oncologists require information about the variants they find in their patient's genetic profile, as well as which treatments are viable options for them. This information, however, is scattered across multiple sites and resources, making it difficult to identify the most appropriate treatment for a patient. This study aims to create a central resource with information about the three most commonly used PGx treatments: Methotrexate, 6-Mercaptopurine, and Asparaginase. Furthermore, it presents the information in the format of a comparative table, to make choosing a suitable drug easier.

Adverse Drug Reactions (ADRs):

In PGx, ADRs are of two types: pharmacokinetic (PK) and pharmacodynamic (PD). The former is a type of adverse reaction in which the issue lies in the metabolism of the drug, while the latter is a biochemical effect of the drug on the body, most often in the form of a toxicity. PK ADRs are harmful as they interfere with the dosage of the drug. Genetic variants of drug-metabolizing enzymes with certain levels can change the size of the dose the patient requires; for example, one variant may metabolize the drug quicker and result in more dosage being required. In PK, however, the patient can experience dangerous toxicities. From this, serious health issues can arise, the patient's quality of life can be greatly affected, and some toxicities can even be life-threatening. To prevent ADRs, it is crucial that oncologists choose treatment for their patients that is best suitable for their genetic profile.

Drug Molecular Mechanisms:

The molecular mechanism of a drug follows the biochemical interactions between the therapeutic drug itself and the biological targets it encounters in its molecular pathway, which are

functioning proteins, such as enzymes. A drug molecular mechanism produces a pharmacological effect. In the case of the three pharmacogenomic ALL treatments studied, each one interacts with proteins involved in the DNA replication of lymphoblasts on a molecular level, to yield apoptosis. However, as each drug has a different molecular pathway, they interact with different functioning proteins. The functioning proteins are encoded by pharmacogenes. Every patient has unique genetic variants of the pharmacogenes, which are what lead to ADRs. Oncologists choose one treatment over another based on whichever one ensures minimum ADRs for the patient, as per testing their genetic profile.

Molecular Mechanism of Drugs

***Methotrexate*:**

Methotrexate is an antimetabolite, which is a type of chemotherapy agent that structurally resembles a crucial component in cell replication in order to disrupt the process. The structure, in the case of methotrexate, is folic acid or Vitamin B9. Folic acid is essential in the biosynthesis of DNA as it makes up the nitrogenous bases of the DNA structure. By mimicking folate, the drug travels through a molecular pathway, in which it competitively inhibits functioning proteins, such as SLC19A1, SLCO1B1, DHR, and TYMS before real folic acid does. This way, DNA replication cannot occur, as methotrexate is in the place of folate. Therefore, the lymphoblasts undergo apoptosis.

***6-Mercaptopurine*:**

6-Mercaptopurine, similarly, is also an antimetabolite. Alternatively however, it is a purine (a type of nitrogenous base) derivative analog, meaning that the structure it resembles is that of an intermediate in the purine metabolism, hypoxanthine in particular. 6-Mercaptopurine is metabolized by drug-metabolizing enzymes such as TPMT and NUDT15. It makes its way through the molecular pathway,

acting as a competitive inhibitor of functioning proteins. By competing with the purine bases, 6-Mercaptopurine corrupts the DNA replication process, therefore, apoptosis occurs.

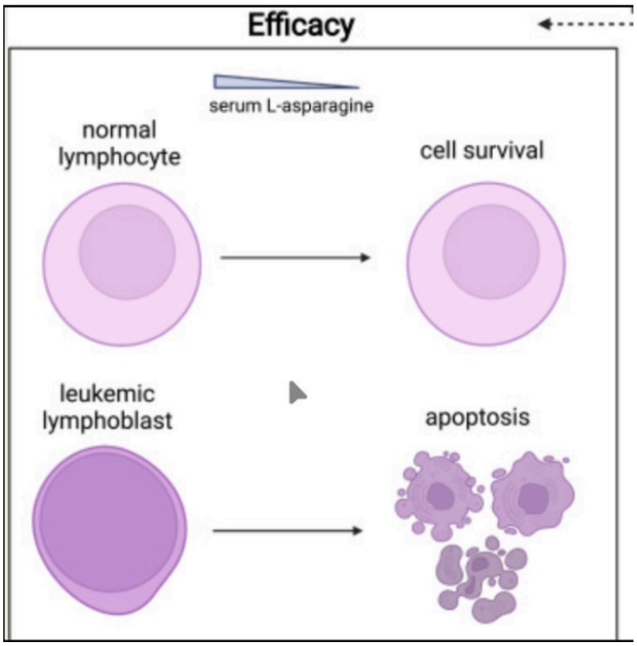

Figure 1. *Impact of decreased L-asparagine levels by Asparaginase on Normal Lymphocytes and Leukemic Lymphoblasts (from K. Juluri, May 30, 2022).* Normal lymphocytes can survive reduced extracellular L-asparagine levels due to their ability to synthesize it intracellularly. However, leukemic lymphoblasts (bottom) undergo apoptosis when extracellular L-asparagine is depleted, as they are unable to produce sufficient amounts on their own.

***Asparaginase*:**

Asparaginase is a treatment that involves starving the lymphoblasts in the body. Regular lymphocytes synthesize L-asparagine, an amino acid crucial for biosynthesis, the process of creating complex components and macromolecules such as DNA. Lymphoblasts, however, cannot produce L-asparagine, and rely on the exogenous supply of it to replicate themselves. The treatment utilizes an L-Asparaginase, an enzyme found in bacteria such as Escherichia Coli, that kills the auxiliary L-asparagine in the extracellular environment. By doing so, the lymphoblasts cannot produce the DNA, and therefore cannot replicate. Consequently, the cell undergoes apoptosis (see: Fig. 1).

Methodology

This study compares the three different types of drugs most commonly used in PGx treatment with one another: Methotrexate, 6-Mercaptopurine, and Asparaginase. A literature review was

conducted for each drug, with information compiled about their molecular mechanisms, the genes important to their molecular pathways (pharmacogenes), and the gene variants of interest.

A primary search was conducted by scientific papers being found through PubMed (searched for using the filters of the last 5 years) published with the key words: Acute Lymphocytic Leukemia and pharmacogenomics. Upon analysis, a secondary data search was conducted to clarify ideas, as well as to provide new information key to the topics at hand. Furthermore, a tertiary search was conducted to find more specific data in concern of gene variants. Scientific papers were found with the key words: [drug name], [gene variant], and adverse reaction. Subsequently, the type of variant was narrowed down to single nucleotide polymorphisms (SNPs), which is a very common type of gene variation, representing a difference in a single nucleotide or DNA building block, located at a specific place on the genome. This choice was made in order for the data to be presented more simply and understandably, as only one type of genetic variant is studied.

The inclusion and exclusion criteria of the study details what qualifications a resource had to or must not have had in order to be applicable to data extraction (see: Fig. 2).

Inclusion Criteria	**Exclusion Criteria**
● Published at most 5 years ago (*only applicable in primary search) ● Published in English ● Published by a reputable source ● Focus on at least one of the following treatments for acute lymphocytic leukemia: ○ methotrexate ○ 6-mercaptopurine ○ asparaginase ● Variants limited to single nucleotide polymorphisms (SNPs)	● Published at least 5 years ago (*only applicable in primary search) ● Published in a foreign language (not English) ● Published by a non-reputable source ● Focus on an illness other than acute lymphocytic leukemia ● Focus on treatments other than methotrexate, 6-mercaptopurine, asparaginase ● Variants outside of SNPs

Figure 2. Inclusion and exclusion criteria applied when considering whether or not to utilize a resource for data extraction.

Data & Analysis:

The study includes a Comparative Data Table of Adverse Reactions to Pharmacogenomic Drugs for ALL (see: Fig. 3).

Legend:	
Antimetabolite	*A type of chemotherapy agent that structurally resembles a part of the DNA replication process, in order to halt it; thus lymphoblasts cannot replicate.*
Analog	*To be analogous in structure to something (ex: methotrexate is a folate analog, because it structurally resembles folate to function as an antimetabolite).*

Comparative Data Table of Adverse Reactions to Pharmacogenomic Drugs for ALL				
Drugs	**Drug Molecular Mechanisms**	**Genes Important to Molecular Pathway (Pharmacogenes)**	**Pharmacogene Variants**	**Adverse Reactions**
Methotrexate (MTX) - folate analog & antimetabolite	MTX structurally resembles folate, which is an essential part of DNA replication. It competitively inhibits the functioning proteins (encoded by pharmacogenes) in the	SLC19A1: encodes protein RFC1 (folate transporter out of liver cells)	rs1051266, AA genotype	Higher plasma folate levels causes MTX to be outcompeted — does not stop DNA replication

	folate's molecular pathway. This is so it can block the DNA replication of lymphoblasts, inducing apoptosis.		rs283895, AA genotype	Prolonged MTX clearance, more MTX remains in the bloodstream—longer exposure leads to hepatotoxicity (liver toxicity)
		SLCO1B1: encodes OATP1B1 (folate transporter into liver cells)	rs4149056, CC genotype	Blocks transport into liver, more MTX remains in the bloodstream—longer exposure leads to hepatotoxicity
			rs2306283, GG genotype	Increases MTX clearance into liver, less MTX exposure—but if the clearance is too fast, then efficacy levels will drop
		DHFR: encodes protein DHFR (enzyme that turns inactive folate into active folate, THF, to make DNA)	rs442767, GG genotype	Leads to severe leukopenia (low white blood cell count)
			rs1650697, AA genotype	Higher risk of ALL relapse (cancer coming back after remission)

			rs408626, CC genotype	Lower risk of leukopenia, lower survival rates
			rs408626, TT genotype	Higher risk of leukopenia, higher survival rates
		TYMS: encodes protein TS (enzyme that catalyzes the biosynthesis of DNA)	rs2790, AA genotype	Higher plasma folate levels causes MTX to be outcompeted — does not stop DNA replication
6-Mercaptopurine - purine analog & antimetabolite	6-Mercaptopurine structurally resembles a purine base called hypoxanthine, which is an essential part of DNA replication. It competitively inhibits the functioning proteins (encoded by pharmacogenes) in the purine's molecular pathway. This is so it can block the DNA replication of lymphoblasts, inducing apoptosis.	TPMT: encodes protein TPMT (inactivates thiopurine drugs, ex: 6-MP, to prevent toxic levels of buildup of antimetabolite)	rs1800460, AA genotype	Critical deficiency— high levels of thiopurine toxicity
			rs1142345, CC genotype	Critical deficiency— high levels of thiopurine toxicity
		NUDT15: encodes protein NUDT15 (breaks down thiopurine drugs before getting incorporated into DNA to prevent toxicity)	rs116855232, TT genotype	Critical deficiency— high levels of thiopurine toxicity
Asparaginase - enzyme acting as an antimetabolite	Asparaginase (or L-Asparaginase) is an enzyme harvested from	GRIA1: type of glutamate receptor in neurons	rs4958351, AA genotype	Hypersensitivity— such as skin rash, erythema, and

	bacteria that breaks down a crucial amino acid called L-asparagine. This amino acid is produced by healthy cells, but not leukemic lymphoblasts, which feed on the supply in the extracellular environment. L-Asparaginase is used to break that supply down, causing the lymphoblasts to starve; this induces apoptosis.	(meditates fast, synaptic communicatio n) and is also expressed in immune cells (like T-cells & B-cells — where ALL originates from)		urticaria

Figure 3. The data table provides information about the drugs investigated, their molecular mechanisms, genes important to their molecular pathway (pharmacogenes), the SNP variants of those pharmacogenes, and the ADRs that can result from the drugs being used in combination with the variants. Additionally, the names of the variants include two details that provide specific information about the SNPs: the former being the location of the SNP in the patient's genome ("rs___"), and the latter being the particular combination of alleles that produce the ADR ("__ genotype").

The pharmacogenes in the molecular pathway of methotrexate are SLC19A1, SLCO1B1, DHFR, and TYMS. SLC19A1 encodes a protein known as RFC1, which transports folate out of liver cells, with the following variants of interest: rs1051266, *AA genotype*—this results in higher plasma folate levels in the body, meaning that there is an abundance of folate that outcompetes the methotrexate, lowering the efficacy of the drug because there is no significant effect on the lymphoblasts' DNA replication; and rs283895, *AA genotype*—this results in the methotrexate taking longer to be cleared out, and as more of the drug remains in the bloodstream, its prolonged exposure to the liver can lead to hepatotoxicity (liver damage). SLCO1B1 encodes a protein known as OATP1B1, which transports folate into liver cells, with the following variants of interest: rs4149056, *CC genotype*—this results in a blockage of methotrexate

transport into the liver cells, causing more of the drug to remain in the bloodstream, potentially leading to hepatotoxicity; and rs2306283, *GG genotype*—this results in an increase of methotrexate being transported into the liver cells, which may prevent hepatotoxicity, but if the clearance is too fast, then the drug's efficacy levels will drop as it does not have enough time to mechanize as it should. DHFR encodes a protein known as DHFR, which is an enzyme that activates otherwise inactive folate called THF, which plays an important role in the biosynthesis of DNA. It has the following variants of interest: rs442767, *GG genotype*—this results in severe leukopenia, a disease in which the patient has a dangerously low white blood cell count, having symptoms such as a much higher susceptibility to illnesses; rs1650697, *AA genotype*—this results in a higher risk of an ALL relapse, meaning that after remission, the cancer will still return; rs408626, *CC genotype*—this results in a lower risk of leukopenia, but lower rates of ALL survival; and rs408626, *TT genotype*—this results in a higher risk of leukopenia, but higher rates of ALL survival. TYMS encodes a protein known as TS, which is an enzyme that catalyzes the biosynthesis of DNA, with the following variant: rs2790, *AA genotype*—this results in higher plasma folate levels in the body, meaning that there is an abundance of folate that outcompetes the methotrexate, lowering the efficacy of the drug because there is no significant effect on the lymphoblasts' DNA replication.

The pharmacogenes in the molecular pathway of 6-mercaptopurine are TPMT and NUDT15. TPMT encodes a protein known as TPMT, which inactivates thiopurine drugs, such as 6-mercaptopurine, to prevent toxic levels of the drug build-up, with the following variants: rs1800460, *AA genotype*—this results in a critical deficiency of the enzyme, leading to high levels of thiopurine-induced toxicity; rs1142345, *CC genotype*—this results in a critical deficiency of the enzyme, leading to high levels of thiopurine-induced toxicity. NUDT15 encodes a protein known as NUDT15, which breaks down thiopurine drugs prior to their incorporation into DNA replication in order to prevent toxicity in the

process, with the following variant: rs116855232, *TT genotype*—this results in a critical deficiency of the enzyme, leading to high levels of thiopurine-induced toxicity.

The pharmacogene in the molecular pathway of asparaginase is GRIA1, which is a type of glutamate receptor in neurons that is also expressed in immune cells, such as T-cells and B-cells (where ALL originates from), with the following variant: rs4958351, *AA genotype*—this results in hypersensitivity ADRs, examples including skin rash, erythema, and urticaria.

Discussion:

To the reviewer's knowledge, this is one of the few first comparative studies evaluating the PGx effects of methotrexate, 6-mercaptopurine, and asparaginase in the treatment of acute lymphocytic leukemia, framed as a central resource for oncologists to use. Genetic variants and corresponding ADRs were compiled from a number of clinical studies. This data was subsequently analyzed and compiled into one source. The analysis was conducted on information about the drugs, their molecular mechanisms, pharmacogenes (the genes essential to their molecular pathway), and the variants of the pharmacogenes. Each variant listed in the data table, with thirteen in total, is an SNP that can cause major adverse effects if the indicated drug is used. It is incredibly important that such information is readily available as a central resource, in order for oncologists to be able to easily identify which treatment is best suitable for their patient. This can improve the quality of the lives of thousands of patients, as well as save the lives of some from fatal ADRs—it is a step forward to improve cancer treatment for patients and oncologists alike. Personalized treatment methods are used because every patient's body and genetic profile is unique, and, as they become more widely used, should have more resources and accessible information about them available. As an extension for the study, variants outside of SNPs can be investigated as well, to provide an even broader range of information. By adding more data, the resource can be applicable to more patients, not just those being treated by

methotrexate, 6-mercaptopurine, and asparaginase. Overall, the future of pharmacogenomic research is promising, because, while complex, it allows oncologists to predict ADRs before treatment even begins.

Conclusion

In conclusion, the three PGx approaches are very promising in the field of precision medicine. This study provides a compilation of genetic variants of pharmacogenes. It contributes to the understanding of the use of PGx treatments in a devastating area of cancer, which causes the deaths of thousands of children in the world. Using PGx, ADRs can occur minimally, as toxicities can be detected prior to treatment with genetic testing. This can save many from fatal reactions, and improve the quality of life of those undergoing treatment. Overall, this study has explored three different PGx drugs, as well as the pharmacogenes and variants they interact with in the body. It provides a central resource for oncologists to use for diagnosis, and can inspire further developments in making PGx research more accessible.

Through this study, young students can have a more clear understanding of such conditions and potentially relate to the lives of so many affected. Hopefully, this study helps raise awareness, evoke empathy, and motivate younger minds to study modern progressive medicine that implements treatments tailored to each patient's genetics.

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available accessed through keywords in a Google search, or if I needed assistance with understanding ideas and concepts in depth.

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