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Review Article

Implementation of pharmacogenetics for treatment of patients with acute lymphoblastic leukemia

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Abstract

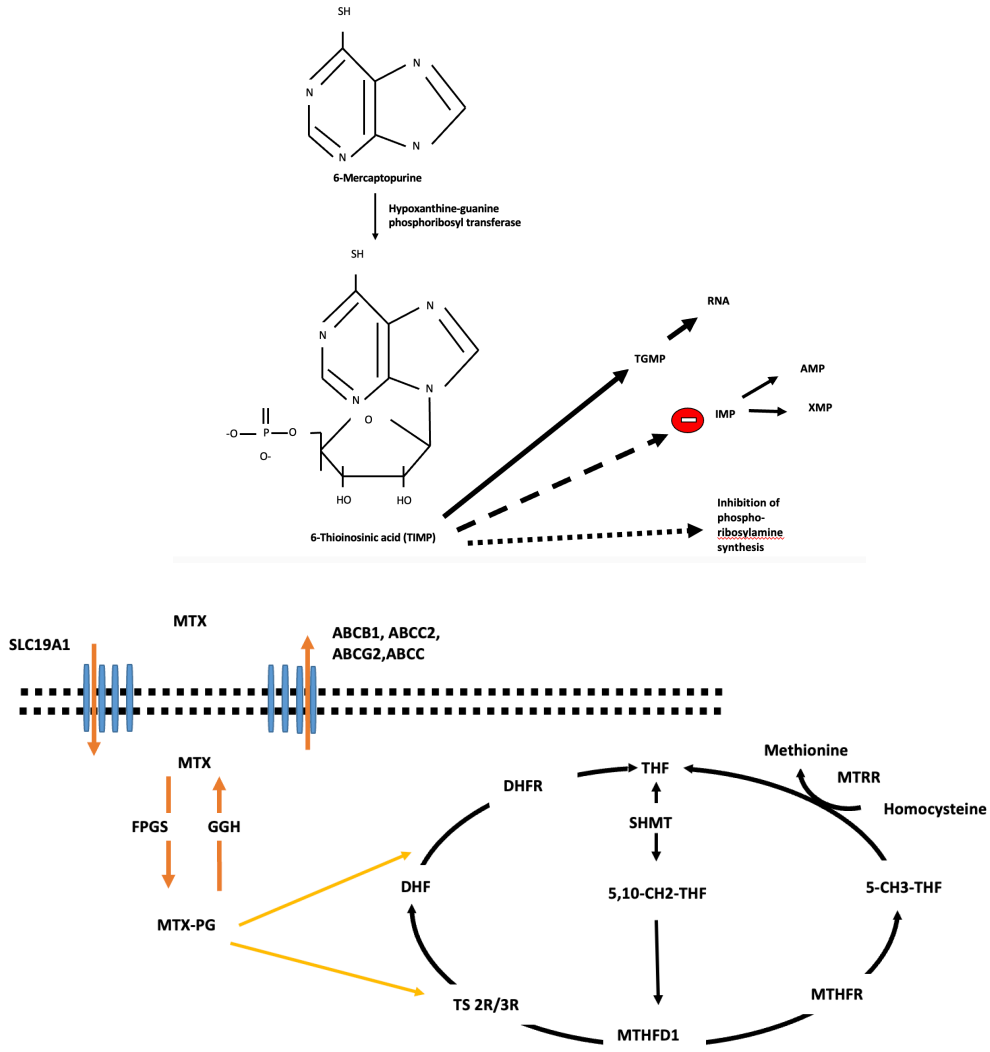
Introduction: Acute lymphoblastic leukemia (ALL) is the most frequent pediatric leukemia; it can be defined according to chromosomic and genomic data. Cytogenetic analyses and determination of chromosomal numbers (such as hypo- or hyperdiploidy) and/or specific chromosomal rearrangements are basic for ALL classification and treatment. Even though cure rates of childhood ALL are at ~95%, pharmacogenetic aspects are of raising importance.

Material and Methods: We have analyzed the literature for ALL subtypes, corresponding therapy options, and pharmacogenetic implications.

Results: Data for ALL subtypes such as B-ALL, T-ALL, Ph-like ALL, DS-ALL, ETP-ALL, BCR-ABL1-like ALL are presented here. The gene polymorphism which lead to metabolizability of 6-MP are ITPA variants (94C>A) and IVS2+21A>C, in conjunction with TPMT (238G>C, TPMT*3B 460G>A and *3C 719A>G and NUDT15 (415C>T). For methotrexate metabolism gene polymorphisms are found for gene *MTHFR* as C677T and A1298C.

Conclusion: In the last decade in many hospital laboratories, pharmacogenetic aspects gain more and more importance. Application of many molecular biology methods provided progress in treatment and diagnosis of ALL patients. Combination therapy is proposed as an alternative to single drug treatments.

Graphical abstract



Keywords

B-ALL, T-ALL, Ph-Like ALL, methotrexate, 6-mercaptopurine

Introduction

Acute lymphoblastic leukemia (ALL) is a rare heterogeneous hematological malignancy, which is characterized by uncontrolled proliferation of premature lymphoid cells. Recently, progress was achieved by developing many strategies to improve the therapeutic results for adults with ALL, by introduction of tyrosine-kinases inhibitor-, CAR- (chimeric antigen receptor), T-cell-, antibody-drug conjugation-, monoclonal and specific antibody-therapies. Besides, ALL is the most common cancer in children, being responsible for about 30% of childhood cancers worldwide (Graiqevci-Uka et al. 2022). Here, cure rates of up to 94% were achieved. However, significant interindividual variability in drug toxicity and treatment outcome was observed. Thus, pharmacogenetics and identification of underlying genetic polymorphisms become more and more important (Evans et al. 2013).

There are different types of protocols for treatment of ALL patients. The typical treatment starts with the induction phase through applying anthracyclines such as doxorubicin (DOX) or daunorubicin (DAU), L-Asparaginase (LASPA), glucocorticoids such as prednisone (PRED) or prednisolone (PRDL), and vinca-alkaloids such as vincristine (VINC) to eradicate leukemic cells. The consolidation phase mainly comprises methotrexate (MTX) with 6-mercaptopurine (6-MP) treatment to kill residual leukemia cells. This phase may be followed by a re-induction cycle with dexamethasone (DEXA) and VINC depending on the

presence of residual cells. Finally, to maintain remission, patients are treated with 6-MP and MTX with rotating cycle of DEXA, VINC or cyclophosphamide (CTX) (Stanulla et al. 2009).

Pharmacogenetics is increasingly taken into consideration in childhood leukemia, specifically ALL (Lopez-Lopez et al. 2014; Mei et al. 2015; Al-Mahayri et al. 2017; Lee et al. 2017; Rudin et al. 2017). Genetic predisposition needs to be considered in single drug admission as well as in combination therapy (e.g. of 6-MP and MTX) and can influence such hepatotoxicity or myelo-suppression (Schmiegelow et al. 2014).

Here, chromosomic and genomic based treatment options of ALL together with pharmacogenetic aspects are reviewed.

Materials and Methods

The studies selected and evaluated here studies were published between 2013-2022. The keywords which were used were "treatment of ALL" and "pharmacogenetics of ALL". We screened approximately 100 papers, and we selected every paper based on gene mutations being important for therapy.

Results and Discussion

Chromosomic and genomic subtypes

ALL is a genetically heterogeneous lymphoid neoplasm derived from T or B-cells. Based on genetic and morphologic characteristics, ALL cases are divided into subgroups (Hoelzer et al. 2016). Diagnosis of ALL is based on bone marrow biopsy and aspiration followed by morphological analysis, flow cytometry immunophenotype, karyotyping, FISH (fluorescence in situ hybridization) and molecular genetics to determine numerical and structural chromosomal aberrations and/or rearrangements on gene level (Faderl et al. 2010).

The German Multicenter Study Group on Adult Acute Lymphoblastic leukemia characterized differences between T- and B- cell ALL based on immunophenotype and molecular genetics. B-ALL comprises approximately 75% of all ALL cases. The B-ALL typically shows expression of cluster differentiation of CD19, CD20, CD22 and CD79a, whereas T-ALL expresses CD3, CD1a, CD2, CD5, CD7, CD56 and TdT. B-ALL has many subtypes, characterized by different chromosomal abnormalities (Faderl et al. 2010; Künz et al. 2022; Moorman et al. 2022). Patients with complex karyotypes and with hypodiploidy/near triploidy have adverse prognoses (Moorman et al. 2022).

The study by Moorman et al. (2022) revealed that patients with complex karyotype and with hypodiploidy/near triploidy show higher rates of relapse and death than other patients.

B-ALL

The ALL patients undergo a generalized treatment. Genomic features of ALL have been classified into several-subtypes (see Table 1).

Two major types with higher risk level of ALL are B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL), and include over thirty distinct subtypes characterized by genetic alternation in germline and somatic cells, which have the ability to cover distinct gene expression profiles (Iacobucci et al. 2017; Pui et al. 2018; Schwab et al. 2018; Gu et al. 2019; Mullighan et al. 2019; Li et al. 2021; Montefiori et al. 2021).

Table 1. The genome subtype of ALL

Type	Characterization	Gene mutations
B-ALL (B-cell acute lymphoblastic leukemia)	highest prevalence of Acute Leukemia	*DUX4; EPOR; ZNF384; ZNF362; NUTM1; ZNF618; ARID5B; CEBPE; GATA3; RUNX1; PAX5; ETV6; IKZF1; TCF3-HLF; KMT2; ETS*
T-ALL (T-cell acute lymphoblastic leukemia)	breakpoints in T-cell receptor gene	*TAL1; TAL2; LYL1; TLX1; TLX3; NKX2-5, LMO1; LMO2; MYB; BCL11B; SP11; CDKN2; FBXW7; GATA3; IKZF1; RUNX1; ETV6*
Ph-like ALL (Philadelphia chromosome–like acute lymphoblastic leukemia)	break-points cluster region in *ABL1* gene	*BCR-ABL1; IGH-CRLF2; P2RY8-CRLF2; JAK1; JAK2; JAK3; TYK2; ABL1; ABL2; CSF1R; LYN; PDGFRA; PDGFRB; FLT3; FGFR1; NTRK3; PTK2B; KMT2A*
DS-ALL (Down Syndrome-Acute Lymphoblastic Leukemia)	children with Down syndrome have high risk for Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia	*ETS; JAK2; P2RY8-CRLF2; RAS; CRLF2; PTPN11*
ETP-ALL (Early T-cell precursor acute lymphoblastic leukemia/lymphoma)	the premature arrest of T-cell differentiation	*RUNX1; IKZF1; ETV6; GATA3; EP300; BRAF; FLT3; IGFR1; JAK1; JAK3; KRAS; NRAS; IL7r; EED; SUZ12; EZH2*
BCR-ABL1-like ALL (BCR-ABL1-like acute lymphoblastic leukemia)	the major features are genetic changes in kinase activities and IL (interleukine) kinase	*ABL1; ABL2; CSFIR; PDGFRB; PDGFRA; CRLF2; EPOR; TSLP; IL2B; TYK2; KRAS; NRAS; NF1; PTNP11; CBL1; BRAF; NTRK3; PTK2B; FLT3; BLNK; FGFR1; DGKH CSF1R; JAK2; CRLF2*
Relapsed Acute Lymphoblastic Leukemia	increased risk for male children, CNS disturbances, T-cell lineage	*NT5C;TP53 Alterations;ETV6/RUNX1 Mutations; BCR-ABL Fusion Gene*

These subtypes are defined by chromosome gains and losses (hyperploidy and hypoploidy), chromosomal rearrangements, such as gene fusions as for example of *DUX4* and *EPOR*, *BXL1B* – rearrangements in T-ALL (Montefiori et al. 2021), and as subtypes with similar gene expression profile but different alternations, such as *BCR-ABL1*-like ALL and *ETV6-RUNX1*-like ALL (Roberts et al. 2012; Roberts et al. 2014; Li et al. 2018; Gu et al. 2019; Kimura et al. 2020; Graiqevci-Uka et al. 2023).

ZNF384 or *ZNF362* are rearranged acute leukemia and are typical for another subtype which is present in approximately 6% of children, and 7.3% of adult, 15% of AYA B-ALL, and 48% of B/myeloid mixed phenotype acute leukemia (MPAL) (Gu et al. 2019; Li et al. 2018; Zaliova et al. 2019; Alexander et al. 2018; Hirabayashi et al. 2019). In *NUTM1* gene (nuclear protein in testis midline carcinoma family 1), mutations are found in approximately <2% of children with B-ALL (Li et al. 2018; Gu et al. 2019; Hormann et al. 2019; McEvoy et al. 2020; Ueno et al. 2020; Boer et al. 2021).

Germline mutations and polymorphism in AT-rich at domain 5B (*ARID5B*), CCAAAT/enhancer binding protein epsilon (*CEBPE*), GATA binding protein 3 (*GATA3*), paired-box containing (*PAX5*), Ets variant gene 6 (*ETV6*) and *IKZF1* gene enhance vulnerability to B-ALL (Perez-Andreu et al. 2013; Perez-Andreu et al. 2015; Wu et al. 2018). Transcription factor 1 (*RUNX1*) can be translocated in association with many tumor suppressor genes, accounting for about 25% of childhood B-ALL (Parker et al. 2008).

Another type of B-ALL is intra-chromosomal amplification of chromosome (iAMP21); this is associated with a constitutional Robertsonian rearrangement being more prevalent in elder children over nine years (Li et al. 2014). Childhood B-ALL also involves translocation of Histone-lysine N-methyltransferase 2A to *KMT2*, most commonly in 3-month-old patients (Pieters et al. 2007). The sPI3K, MEK and Ras signaling pathways are shown to play pivotal role in enhancing mutation of *KMT-2A* gene. Translocation of this gene is involved in different epigenetic processes, such as histone methylation or histone deacetylation. Hence, decitabine, 5-azacytidine, panobinostat etc. that block epigenetic modulation have been suggested as suitable therapeutics targeting patients with B-ALL.

DS (Down Syndrome -ALL)

DS-ALL refers to Acute Lymphoblastic Leukemia (ALL) that is associated with Down syndrome (DS). Down syndrome can be associated with B-ALL, and children with ALL and DS have very poor outcomes (Izraeli et al. 2014; Behluli et al. 2022). Here are the key points regarding DS-ALL based on the provided search results:

1) Unique characteristics: DS-ALL presents unique characteristics compared to non-DS ALL (NDS-ALL). In DS, the increased risk of ALL is primarily limited to the B-cell precursor phenotype. Additionally, acquired polysomy of chromosome 21 is predominantly found in B-cell precursor ALL in children without DS (Izraeli et al. 2014).

2) Genetic variability: DS-ALL is not a single biological entity but rather exhibits heterogeneity confirmed by gene expression and cytogenetic analyses. Notably, common cytogenetic subgroups and unfavorable translocations like BCR-ABL and MLL-AF4 are less common in DS-ALL. Approximately 40% of DS-ALL cases have a normal karyotype compared to only 7% of NDS-ALL cases (Izraeli et al. 2014).

3) Cytokine receptor abnormalities: Abnormal expression of the cytokine receptor CRLF2 has been identified in around 60% of DS-ALL cases. This abnormality, together with other mutations downstream, provides a pathway relevant to a significant proportion of DS-ALL cases that may be targeted by specific inhibitors (Izraeli et al. 2014).

4) Treatment implications: The genetic differences between DS and NDS ALL have implications for therapy outcomes. Stem cell transplant (SCT) can be considered for DS-ALL patients in good general health with a good response to relapse induction chemotherapy. A radiation-free approach may be preferred due to concerns about central nervous system toxicity (Izraeli et al. 2014; Davis et al. 2023; Duffield et al. 2023). [Understanding the distinct features of DS-ALL, including genetic variations and treatment implications, is crucial for optimizing therapeutic strategies and improving outcomes for individuals with DS-ALL.

ETP-acute lymphoblastic leukemia (ETP-ALL)

Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is a rare and distinct subtype of T-cell acute lymphoblastic leukemia (T-ALL) characterized by specific genetic and immunophenotypic features. Here are the key insights based on the provided search results:

1) Immunophenotypic characteristics: ETP-ALL is identified by a unique immunophenotypic signature, including CD7+, with CD34+ and/or CD13+/CD33+, while being negative for CD1, CD4, and CD8. This specific immunophenotypic profile aids in the accurate identification of ETP-ALL cases, with 94% specificity (Tarantini et al. 2021).

2) Genetic aberrations: ETP-ALL exhibits a distinct genetic landscape compared to other T-ALL subtypes. Mutations in genes encoding transcription factors, kinase signaling molecules, and epigenetic modifiers are common in ETP-ALL. Notably, mutations in *FLT3, DMNT3A, IL7R, JAK3, RUNX1, EZH2,* and *EED* are more prevalent in ETP-ALL cases (Sin et al. 2021).

3) Chromosomal abnormalities: While no clear association with specific chromosomal abnormalities is found in ETP-ALL, the disease is characterized by high genomic instability. Some reported chromosomal aberrations include a slightly higher frequency of deletion 13q and a translocation t(2;14)(q22;q32) associated with *ZEB2* deregulation (Tarantini et al. 2021).

4) Clinical aggressiveness: ETP-ALL is known for its clinical aggressiveness and historically poor outcomes. The unique genetic and immunophenotypic features contribute to the challenging nature of this subtype. Allogeneic stem cell transplant (SCT) has shown potential benefits in improving outcomes for ETP-ALL patients (Jain et al. 2016). Understanding the distinct characteristics of ETP-ALL, including its immunophenotypic profile, genetic mutations, and clinical behavior, is crucial for tailored treatment approaches and prognostication in individuals diagnosed with this rare subtype of T-cell acute lymphoblastic leukemia.

T-ALL

It is known that T-ALL cells express a subset of T-cell markers such as CD3, cyCD3, CD2, CD5, CD7, CD8 (Iacobucci et al. 2021). The different cases of T-ALL may be subclassified according to aberrant expression and dysregulated pathway of different transcription factors such as basic helix-loop-helix (bHLH) factors (TAL1, TAL2, LYL1), homeobox genes (*TLX1* (*HOX11*), *TLX3* (*HOX11L2*), *NKX2-5*, *HOXA*), *LMO1*, *LMO2*, *MYB*, *BCL11B* and *SPI1* (Liu et al. 2017; Seki et al. 2017; Montefiori et al. 2021).

These subtypes are defined with expression profiles by WGS or microarray; however, almost half of these leukemia-initiating alterations in T-ALL show intergenic breakpoints (Roberts et al. 2016; Liu et al. 2017).

Compared to B-ALL, T-ALL has well-defined chemotherapy guidelines, including immunophenotype targets with the potential to minimize T-ALL pathology (Vora et al. 2016). Mutations observed in T-ALL patients affect *NOTCH1*, *CDKN2* (cyclin dependent kinase inhibitor 2A) and F-box WD repeat domain containing 7 (*FBXW7*) which stimulate the PI3K/AKT signaling pathway during cell proliferation of cancer cells (Paganin and Ferrando 2011). Chromosomal rearrangements are found to be very common in T-ALL; T-cell receptors fused to "T-cell leukemia homeobox 1-T-cell receptor δ (*TLX1-TCRδ*)" and *STIL-TAL1* oncogenes (Tasian et al. 2015) are observed. Mutations in gene *TLX* have distinct connection with X-chromosome, and occur more often in pediatric male population. X-chromosome's deletion at the plant homeodomain finger 6 (*PHF6*) gene plays pivotal role during tumor suppression, histone remodeling and prevent cell proliferation via its direct effect on transcription (Van Vlierberghe et al. 2010).

An "early T-cell precursor" (ETP) cell subtype has also been shown to have influence at up-regulation of immune reactivity; increasing cluster differentiation 3 (CD3) expression and suppressing CD1a and CD (Coustan-Smith et al. 2009). The primary gene mutation for ETP were in *GATA3*, *IKZF1*, *RUNX1* and *ETV6*, responsibly for myeloid and stem cell development (Pui 2015).

Ph-like ALL

It is known that 10% of all ALL belong to the category of Philadelphia chromosome-like (*BCR-ABL1*-like) or better represented as "Ph-like" group. Mutation in the breakpoint region - Abelson murine leukemia gene 1 – is shown to cause resistance to the treatment with tyrosine kinase inhibitors. In the Brazilian patients, there were studies on *BCR-ABL1* gene mutation. In 193 patients, two simultaneous mutations (E189G/V299L and E255K/T315I) were observed in 2/5 of patients while other mutations were found in sequential samples of the other three patients (Y253Y/T315I, T315I/E255K and E255K/T315I). This molecular characterization contributes to the identification of resistance profile to TKI inhibition in Brazilian patients (Costa et al. 2018). Tanasi et al. 2019 dentified the ABL-class fusion was identified at initial diagnosis work up and TKI was introduced during front line treatment. In 5 patients, ABL-class fusions were diagnosed at relapse and TKI was introduced in association with salvage therapy This is made by decision of physicians for TKI, TKI dosage and combination also. Fourteen patients were treated with imatinib, 9 with dasatinib, and one – with ponatinib. Three patients first were treated with imatinib and then were switched to dasatinib during the first phase of treatment. The same group reported on the largest cohort of patients with ABL kinase rearrangement exposed to frontline tyrosine kinase inhibitor (TKI) therapy, and showed promising outcomes, reminiscent of those observed in early treatment with imatinib and chemotherapy combination in Ph-ALL patients.

The most common signaling pathway mutated is JAK/STAT; but other alternations are found and are grouped into three types such as: 1) JAK/STAT alteration including mutation in cytokine receptor, e.g. *CRLF2* and *IL7R*; gene rearrangement deregulating cytokine receptor expression, e.g., *IGH-CRLF2* and *P2RY8-CRLF2* (Mullighan et al. 2009; Yoda et al. 2009; Hertzberg et al. 2010; Russell et al. 2017); gene fusion or mutated activated kinases, e.g., *JAK1*, *JAK2*, *JAK3*, *TYK2*; and rearrangement of truncated cytokine receptor expression such as cryptic *EPOR* rearrangement (Iacobucci et al. 2016); 2) fusion involving other genes such as ABL-class genes (*ABL1*, *ABL2*, *CSF1R*, *LYN*, *PDGFRA*, *PDGFRB*) and 3) less common fusion genes such as *FLT3*, *FGFR1*, *NTRK3*, *PTK2B* (Iacobucci et al. 2017; Roberts 2017).

The study by Raimondi et al. (1990) show mutation of TKI and cytokine receptor genes. The JAK signaling pathway and gene fusion such as "platelet-derived growth factor receptor beta (PDGFRB)", ABL1, ABL2 and colony stimulation factor 1 receptor (CSF1R) show mutation, as well as gene mutation.

Overall, the optimal therapy has not yet been defined for Ph-like ALL, and prospective trials evaluating TKIs in combination with chemotherapy are currently underway.

Relapsed ALL

Relapsed ALL are a challenge for treatment of children. Until today, treatment options have been limited to incisive cytotoxic chemotherapy with or without site directed radiotherapy and allogenic hematopoietic stem cell transplantation (HSCT) (Hunger and Raetz 2020). In the past decade, several immunotherapeutic methods were developed, changing the treatment of children with relapsed ALL. Currently, the incorporation of immunotherapeutics is being explored as a treatment approach into salvage regiments, and survival rates and side effects are being investigated. This treatment may offer real promise for less toxic and very effective therapy for children with relapsed ALL (Hu et al. 2022; Lv et al. 2022), Figure 1.

Genetic polymorphism of ALL

The most reported genetic polymorphism being of potential importance for personalized medicine are genes *NUDT15* c.415 C>T (15*3), *TPMT*3C, *ITPA* c.94 C>A, and *MRP4* c.2269 C>T (Pai et al. 2021). Also, it has been shown that 6-mercaptopurine toxicity is influenced by genetic polymorphism of genes *ITPA* 94C>A and *IVS2*+21A>C, *TMPT*2 238G>C, *TPMT*3B460G>A and *3C719A>G, and *NUDT15* 415C>T (Moradveisi et al. 2019; Mao et al. 2021).

Methotrexate

MTX is a folate analog which is a widely used form for cancer treatment (Chabner et al. 1985; Schmiegelow et al. 2014). MTX is pro-drug, being processed by

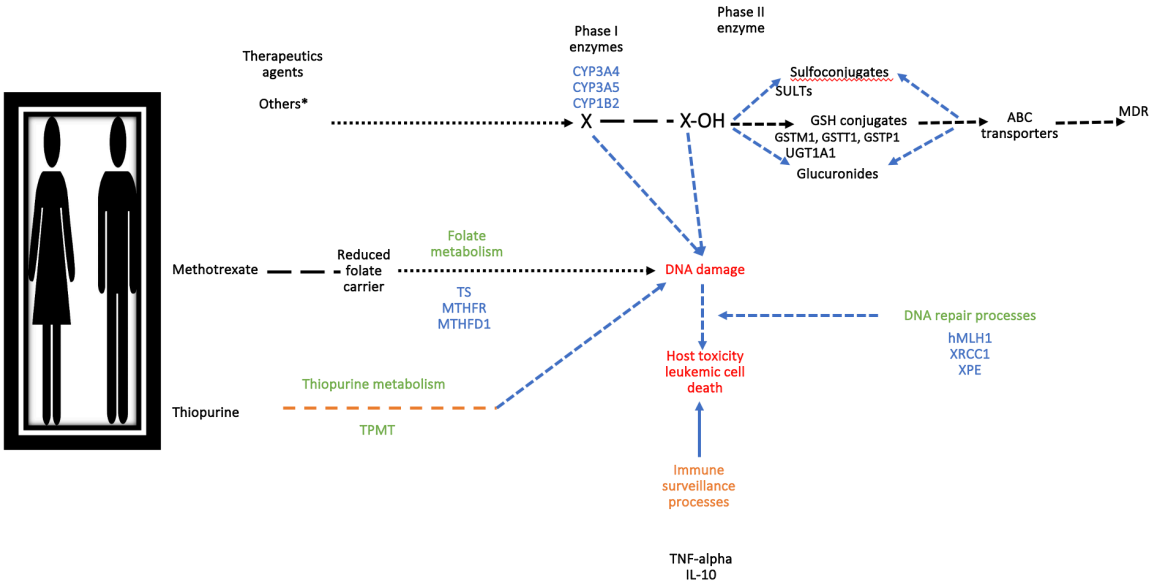


Figure 1. Genetic and other factors which are reported to be involved and to have impact on chemotherapy efficacy and toxicity. ***Note:*** ABC – ATP binding cassette. GSH – Glutathione –s-transferase; hMLH1 – mutL homolog 1; MTHFD1 – Methylentetrahydrofolate dehydrogenase; MTHFR – Methylentetrahydrofolate reductase; MDR – multidrug resistance protein; SULT – sulfotransferase; TS – Thymydilate synthase; TPMT – Thiopurine methyl transferase; UGT – UDP glucuronyl transferase; RFC – Reduced folate carrier; XPE – damage-specific DNA binding protein 1; XRCC1 – X-ray repair complementing defective repair in Chinese hamster cell 1.

folylpolyglutamyl synthetase (FPGS) to gamma-linked glutamic acid residues. Methotrexate (MTX) is the most effective drug which is used for treatment of pediatric ALL patients which have better overall survival. Delayed MTX clearance can lead to prolonged, elevated exposure, causing increased risks for nephrotoxicity, mucositis, seizures, and neutropenia. So far several genes have been identified which are involved in the MTX clearance. Taylor et al. (2021) during the search for genes involved in the MTX metabolism found that 24 different genes are involved in the folate transport pathway, but the only one gene that reliably demonstrate an effect on MTX is *SLCO1B1* (reviewed by Taylor et al. 2021). Ramalingam et al. (2022) show that *SLC19A1* gene facilitates cyclic dinucleotide import and folate reductions and help for better management MTX in the ALL-patients who are treated with this type of drug.

Shen et al. (2021) analyzed the effects of *MTHFR* C677T and A1298C polymorphisms on MTX elimination and toxicities. It was shown that patients with the genotype *MTHFR* C677T TT could tolerate a significantly higher MTX dose than patients who have genotype CC/CT. But, in the patients with genotype C677T TT, the risk for hypokalemia was shown to increase (1.369 to CC and 1.409 to CT types). The rate of MTX infusion in the patients who have the genotype *MTHFR* A1298C AC is shown to be slightly lower than in the patients who have genotype CC or AA. The patients with the genotype A1298C AA were shown to have a higher risk for hepatotoxicity – approximately 1.405-fold than those with the AC genotype (P>0.05) (Shen et al. 2021).

The patients who had genotype C677T after treatment with MTX were shown to have oral mucositis, leucopenia, and thrombocytopenia, while patients with genotype A1298C were shown to have a low risk for vomiting, but were more likely to develop anemia and leucopenia (Lu et al. 2021).

The polymorphism of MTHFR C677T and A1298C was shown to lack marker for MTX-related toxicity and/or outcome in pediatric ALL (Umerez et al. 2017).

6-Mercaptopurine

Mercaptopurine is well established for treatment of a wide range of diseases such as leukemia and other inflammatory diseases in general. This drug has a quick rate of absorption and elimination, but it has shown to have different effects on individuals (Perez-Andreu et al. 2013). Seven genes (*NUDT15*, *SUCLA2*, *TPMT*, *IPTA*, *IMPGH1*, *MTHFR*, *PACSIN2*, and *MRP4*) are associated with mercaptopurine intolerance (Zhou et al. 2020; Wang et al. 2021). *NUDT15* (rs116855232) and *IMPGH1* (rs2278293) were associated with a 5.50-fold and 5.80-fold higher risk of leukopenia, respectively (Zhou et al. 2020).

The data from the study of Moradveisi et al. (2019) confirm the important role of *TPMT*, *NUDT15*, and *ITPA* genes in the 6-MP intolerance in Middle Eastern countries for children diagnosed with ALL. Based on the higher frequency of ITPA gene variants found in the study by Maradveisi et al. and higher significant association of genes with 6-MP dose intensity mentioned above, the same author recommends that physicians must consider genotyping of *ITPA* variants (94C>A (rs1127354)) and IVS2+21A>C (rs7270101)), in conjunction with TPMT (238G>C (rs1800462), TPMT*3B 460G>A (rs1800460) and *3C 719A>G (rs1142345)) and NUDT15 (415C>T (rs116855232)) prior to 6-MP therapy in the children diagnosed with ALL (Moradveisi et al. 2019).

Hao et al. (2021) showed the genetic polymorphism of *TMPT* gene (CC genotype for both *TPMT**2 and *TPMT**3B) in the ALL patients. The genetic polymorphism for TPMT*3C (TT and TC) reach 96.76% and 3.24%, respectively. The allele frequency was 1.62% for *TPMT**3C and *NUDT15* has an effect on the tolerance of 6-MP in the treatment of adult ALL (Hao et al. 2021), Figure 2.

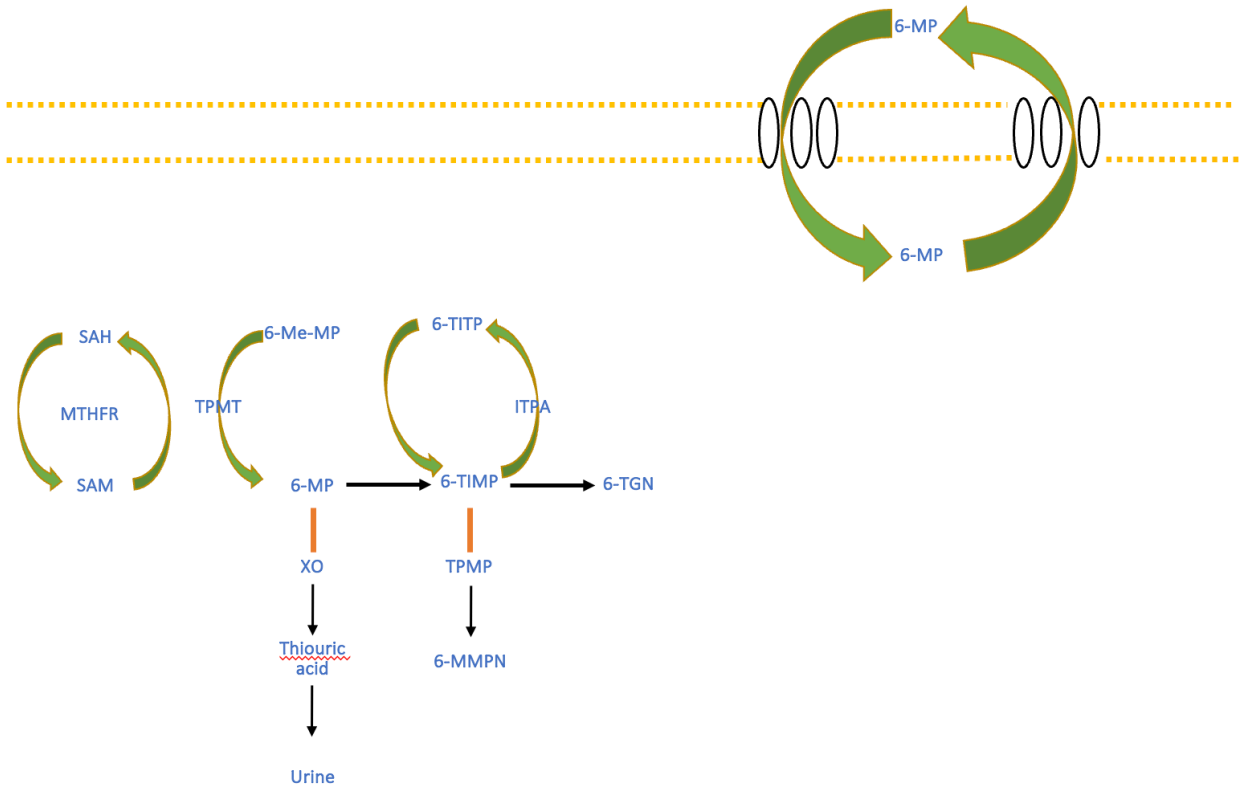


Figure 2. The intercellular pathway of 6-MP (6-mercaptopurine). ***Note:*** SAM – S-adenosylmethionine; SAH-S adenosylmethionine; SAH – S-adenosylhomocysteine; TPMT – thiopurine S-methyltransferase; XO – xanthine oxidase; 6-Me-MP – 6-methyl-mercaptopurine; 6-TIMP – 6-thioinosine triphosphate; ITPA – inosine triphosphate pyrophosphatase; 6-MMPN – 6-methyl-mercaptopurine nucleoside; 6-TGN – 6-thioguanine nucleoside.

Dexamethasone and ALL pharmacogenetics

Dexamethasone is known to be a very important component for treatment of childhood with acute lymphoblastic leukemia (ALL). Such genes as *ABCB1*, *GSTM1*, *GSTT1*, *BCL2*, *BCL2L11*, and *MCL1* have a potential effect on dexamethasone treatment of ALL patients (Jackson et al. 2016; Jackson et al. 2019; Zou et al. 2021).

The first five days of treatment of children with dexamethasone showed an increase in their nighttime sleeping; and during the daytime, the napping was observed in the young children with ALL. The increases in sleep duration return to baseline one day after the discontinuation of dexamethasone (Rosen et al. 2015).

Cytarabine

Cytarabine is a type of drug which is known by brand name Ara C. and in the activation form is as 1-β-D-arabinofuranoxyl cytosine-5'-triphosphate, and in a dose of 100 mg/m^2 is a well established drug for leukemia (Krajinovic et al. 2002). Cytarabine has an ability to block DNA replication via inhibition of DNA polymerases (Wiley et al. 1982).

It is shown that Cytarabine (Ara-c) and EIP synergistically reduce viability of ALL cells with high ERG expression, which may be achieved by promoting their apoptosis and inhibiting their nesting (Cheng et al. 2021). Individual variability among patients diagnosed with leukemia appears to be associated with accumulation of Ara-CTP due to genetic variants of metabolic enzymes. In review by Di Francia et al. (2021), they report about response association of cytarabine and new drugs which are optimized in pharmacokinetics aspects. The study of candidate genes is focused on the sequence variation, alternative splicing, and expression of the key cytarabine gene pathways, including *SCL29A1, DCK, CDA,* and *NT5C2*. The SNPs (single nucleotide polymorphism) in the coding region of these genes have shown to participate in the protein production with amino acid changes (Lamba, 2009; Cao et al. 2018; Zhu et al. 2018). The DCK (deoxycytidine kinase) plays the pivotal role in activation of Cytarabine; this gene has several SNPs (-125G>T, -201C>T, -289T>A, -360C>G, and -740G>C) and three others are non-synonymous coding changes Ile24Val, Ala119Gly, and Pro122Ser in activation of cytarabine and metabolization (Lamba et al. 2007). Also Cytarabine catabolism is made during the deamination process, which involves CDA and CMPD enzymes, and dephosphorylation by NT5C family enzymes.

Conclusion

In conclusion of this review, we report about the

subtypes different methods for diagnosis and treatment of patients with ALL, and genes which are involved in drug administration together with their polymorphisms. Based on literature which we have reviewed, we can see that in many cases gene fusions in all types of ALL. Some of literature resource them have been focused on the treatment of ALL patients (B-ALL, T-ALL and Ph-Like ALL) and genes which are responsible for these types of ALL. In this review, we have considered all data published together, and we show the growth evidence of the involvement of drugs such as MTX, 6-MP, Cytarabine, and Dexamethasone in the treatment of patients diagnosed with ALL. On the other hand, considering the polymorphism for B-ALL, T-ALL and Ph-like ALL treatment and toxicities, it would be very interesting to analyze gene polymorphism such as *DUX4* and *EPOR*, *BXL11B, BCR-ABL1*-like ALL, *ETV6-RUNX* (*TLX1* (*HOX11*), *TLX3* (*HOX11L2*), *NKX2-5*, *HOXA*), *LMO1*, *LMO2*, *MYB*, *BCL11B* and *SPI1*. The development field of pharmacogenetics has started to produce the promise results and genetic variants have great potential to be used as biomarkers for further studies, which are very important to increase the power of patients cure diagnosed before.

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

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