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Genomics and pharmacogenomics of pediatric acute lymphoblastic leukemia

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is a prevalent form of pediatric cancer that accounts for 70–80% of all leukemias. Genome-based analysis, exome sequencing, transcriptomics and proteomics have provided insight into genetic classification of ALL and helped identify novel subtypes of the disease. B and T cell-based ALL are two well-characterized genomic subtypes, significantly marked by bone marrow disorders, along with mutations in trisomy 21 and T53. The other ALLs include Early T-cell precursor ALL, Philadelphia chromosome-like ALL, Down syndrome-associated ALL and Relapsed ALL. Chromosomal number forms a basis of classification, such as, hypodiploid ALL, near-haploid, low-hypodiploid, high-hypodiploid and hypodiploid-ALL. Advances in therapies targeting ALL have been noteworthy, with significant pre-clinical and clinical studies on drug pharmacokinetics and pharmacodynamics. Methotrexate and 6-mercaptopurine are leading drugs with best demonstrated efficacies against childhood ALL. The drugs in combination, following dose titration, have also been used for maintenance therapy. Methotrexate-polyglutamate is a key metabolite that specifically targets the disease pathogenesis, and 6-thioguanine nucleotides, derived from 6-mercaptopurine, impede replication and transcription processes, inducing cytotoxicity. Additionally, glucocorticoids, asparaginase, anthracycline, vincristine and cytarabine that trans-repress gene expression, deprives cells of asparagine, triggers cell cycle arrest, influences cytochrome-P450 polymorphism and inhibits DNA polymerase, respectively, have been used in chemotherapy in ALL patients. Overall, this review covers the progress in genome technology related to different sub-types of ALL and pharmacokinetics and pharmacodynamics of its medications. It also enlightens adverse effects of current drugs, and emphasizes the necessity of genome-wide association studies for restricting childhood ALL.

1. Introduction

Acute Lymphoblastic Leukemia (ALL) is the predominant form of cancer in children. Although clinically manageable, its recurrence is often deadly, resulting in early age mortality. A major focus for ALL-targeted research is on childhood symptoms and the pediatric manifestations. Wide ranging efforts have been made to better understand pediatric ALL and, these have resulted in considerably improved insights into ALL's genetic classification and identification of ALL subtypes. There have also been efforts to improve therapies against ALL

Abbreviations: ABC, ATP-binding cassette transporters; ADSL, Adenylosuccinate Lyase; ALL, Acute Lymphoblastic Leukemia; ARID5B, AT-rich interaction domain 5B; B-ALL, B-Cell Acute Lymphoblastic Leukemia; BCR-ABL1, Breakpoint Cluster Region-ABelson murine Leukemia viral oncogene homolog 1; BMI1-PIP4K2A, B lymphoma Mo-MLV insertion region 1-Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Alpha; CD3, Cluster of Differentiation-3; CDKN2A, Cyclin Dependent Kinase Inhibitor 2A; CDKN2A, Cyclin-Dependent Kinase Inhibitor 2A; CDKN2B, Cyclin Dependent Kinase Inhibitor 2B; CEBPE, CCAAT/Enhancer Binding Protein Epsilon; CNS, Central Nervous System; CREBBP, cAMP-Response Element Binding Protein; CRLF2, Cytokine Receptor-Like Factor 2; CSF1R, Colony Stimulating Factor 1 Receptor; DARS, Aspartyl-tRNA synthetase; DHFR, Dihydrofolate Reductase; DS-ALL, Down syndrome associated ALL; EFS, Event-Free Survival; ETP, Early T-cell Precursor; ETS, Erythroblast Transformation-Specific; ETV6, Ets Variant Gene 6; FBXW7, F-box and WD repeat domain containing 7; FISH, Fluorescence in situ hybridization; FLT3, fms-related tyrosine kinase 3 receptor; FPGS, FolylPolyGlutamate Synthetase; GATA3, GATA Binding Protein 3; GI, GastroIntestinal; GSTs, Glutathione S-Transferases; IAMP21, Intra-chromosomal Amplification of Chromosome; IGH, Immunoglobulin heavy locus; IKZF1, IKAROS family zinc finger 1; IMPA2, Inositol Monophosphatase 2; KRAS, Ki-ras proto oncogene; MRD, Minimal Residual Disease; MTHFR, 5,10-MethyleneTetraHydroFolate Reductase; MTXPGs, MTX metabolism and Poly(γ-Glutamate) forms; P2RY8, Purinergic Receptor P2Y8; PAX5, Paired-Box Containing; PBX1, TCF3-Pre-B cell leukemia transcription factor-1; PDGFRB, Platelet-Derived Growth Factor Receptor Beta; PHF6, Plant Homeodomain Finger 6; PTPN11, Tyrosine-protein phosphatase non-receptor type 11; RASSF4, Ras Association Domain Family member 4; RFC-SLC19A1, Reduced Folate Carrier- Solute Carrier Family 19 Member 1; RUNX1, Runt-related transcription factor 1; SETD2, SET domain containing 2; SLC39A6, Solute carrier family 39 member 6; SLCO1B, Solute carrier organic anion transporter family member 1B1; T-ALL, T-cell ALL; TCF3-HLF, Transcription factor 3-Hepatic leukemia factor gene; TGNs, ThioGuanine Nucleotides; TLX1-TCRδ, T-cell leukemia homeobox 1–T-cell receptor δ; TPMT, Thiopurine S-MethylTransferase; TYMS, Thymidylate Synthase; UGT, UDP-Glucuronosyl Transferase; WBC, White Blood Cell

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and a number of drugs, and the combinations thereof, are currently being used in clinics. In addition, a number of drugs are in different stages of clinical trials. These are exciting developments as the drugs against ALL represent many different classes. This review article undertakes to comprehensively uncover the progress made towards the genetics of the disease and its various subtypes; it also discusses the various therapies, both experimental and clinical, that are helping us fight against pediatric ALL. A major focus is on the pharmacokinetics and pharmacodynamics of various drugs. It is envisioned that this review article will summarize the progress made so far, and will encourage researchers and clinicians to employ cutting edge research and methods to keep making the progress in the fight against ALL.

The annual prevelance of ALL is around 3000 pediatric cases in the United States (Tasian et al., 2015). The disease often results in severely unhealthy condition at adulthood (Roberts and Mullighan, 2015). Treatments in children and young adults for ALL have resulted in a five-year disease free state with a cure rate of about 85–90% (Inaba et al., 2013). However, recurrence of the disease, which occurs in about 15–20% of children, culminated in early age mortality (Ko et al., 2010). ALL is less frequently reported in adults, and hence the major therapeutics target childhood symptoms and manifestations of the disease (Stock, 2010). The age of the patients and white blood cell (WBC) count played important role in speculating the disease consequences, and disease prediction appeared more convincing and consistent for children compared to adult and aged patients (Pui et al., 2012). Standard risk parameters stipulated by the National Cancer Institute - Rome included an age group of 1–10 years, and a high risk was for above 10 years, with a WBC of $< 50{,}000/\mu L$ and $> 50{,}000/\mu L$ respectively (Smith et al., 1996).

Genetic reasons played a key role for childhood prevalence of ALL compared to adults. With the help of microarray-based approaches, DNA copy number studies, next generation sequencing, whole genome sequencing, exome sequencing, transcriptomics, epigenomics and genetic mutation analysis, causes and progression of childhood ALL have been identified, to a certain extent (Pui, 2015). Although every sequencing technique bears certain benefits and disadvantages, nonetheless, they all have marked contribution towards understanding the disease generation, advancement, prognosis and cure. The key genetic alterations comprise single nucleotide polymorphisms (SNPs), duplication of entire chromosomes, genetic copy number variation and genetic mutations involving deletions, point mutations and insertions (Yang et al., 2010). The others that include tumor-specific genetic changes involve movement of chromosomal segments, loss of heterozygosity and reduction in surrounding chromosomal region, and uniparental disomy (Cheok et al., 2009). Aberrant DNA hypermethylation and methylation of CpG islands, culminating in epigenetic changes, have also been detected in childhood ALL patients (Roberts and Mullighan, 2015). Variations in DNA replication, apoptosis, cell proliferation and differentiation, altered expression of cell cycle and cytoskeletal proteins and changes in cell signaling mechanisms are some of the key reasons triggering ALL (Cheok et al., 2009). The lymphoblastic lymphoma results from either B-cell or T-cell origin, with close but un-identical manifestations (Bassan et al., 2016). In the current review, we summarize the genomics and pharmacogenomics of ALL. We scrutinize the genomic sequencing methods, genetic aberrations and subtypes of leukemia, ploidy-based classifications, pharmacogenomic studies linked to treatment of childhood ALL and therapeutic usefulness and toxicity.

2. Genome sequencing methods in ALL

There are several genome sequencing methods for pediatric ALL (Table 1). Targeted approach in sequencing precisely aims at identifying hotspot mutations at the specific site of interest (Taylor et al., 2007).

2.1. Targeted sequencing

This sequencing method appears particularly useful for recognizing sequence mutations in genes, but however, fails to spot rearrangements and changes in copy numbers (Papaemmanuil et al., 2014).

2.2. Exome sequencing

This sequencing method is largely used for proving sequence mutations and is a less costly technique for spotting genetic mutations during ALL (De Keersmaecker et al., 2013). The technique captures and sequences the coding exons along with the promoter and non-coding domains of the genome. Exome sequencing also spots the genetic copy number variations within the gene sequences captured. However, the method has some disadvantages, being incapable of recognizing deletion, insertion and structural rearrangement mutations that are well-reported to promote tumor formation and malignancy (Zhang et al., 2012). Hence, exome sequencing appears to fall short of detecting clinically significant genomic mutations.

2.3. Transcriptome analysis

This sequencing method (or basically mRNA sequencing technique) spots the protein-coding transcripts and tiny non-coding transcript alterations in enhancer regions that play a key regulatory role in leukemogenesis (Trimarchi et al., 2014). Transcriptome analysis is useful for recognizing the frequently seen chimeric fusion genes in ALL and new genetic isoforms within the specified RNA sequences (Herranz et al., 2014). Unlike exome sequencing, mRNA sequencing method recognizes genetic rearrangements and sequence mutations. Although comparatively a costlier method, sequencing of the whole genome plays a vital role in identifying all rearrangements and genetic mutations (Meyerson et al., 2010). Transcriptome analysis method comprises a comparative analysis and bears extensive benefits as it helps differentiating whether the disease resulted from aberrant inheritance with altered genes and chromosomes, somatic or germline mutations (Ma et al., 2015). The relative or comparative examination for recognizing somatic variants in whole genome sequencing entails tumorous and non-tumorous genome sequences, and the latter is again compared to a reference genome through genome re-sequencing that aids in spotting germline variants (Roberts and Mullighan, 2015).

2.4. Whole genome sequencing

This sequencing method generally detects high-frequency variants (Huether et al., 2014). The tumor genome has been generally compared to the matched non-tumor genome to identify somatic variants, and the non-tumor sample undergoes comparison to a reference genome to identify germline variants (Muhlbacher et al., 2014). The most precise and accepted technique for genomic sequence analysis is the whole genome sequencing; however, the method fails to identify promoter regions, GC-rich domains and any complex genomic sequences. Additionally, the extensively lengthy human genome sequence, requiring significantly high sequencing procedures, impedes a correct sequencing. From this angle, the exome sequencing appears advantageous above the whole genome sequencing. These genomic sequencing techniques ultimately help identifying new genetic isoforms coding for novel subtypes of ALL that have marked genomic alterations compared to the normal genome. The methods point towards clonal heterogeneity in ALL and its correlation with resistance to specific agents conferring therapeutic resistance. The genomic sequencing gives an indication of disease vulnerability, and also enlightens the approach that supports disease diagnosis, prediction and remediation (Roberts and Mullighan, 2015). The techniques help identifying the altered genomic sequences. The remarkable mutated genomic sequences include (1) Philadelphia chromosome [Ph]-like ALL that involves rearrangements and fusions in