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Review Article **Pediatric**

Personalized Medicine Approaches for Pediatric Leukemia: Developing Targeted Therapies Based on Genetic Profiles

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Abstract

Leukemia remains the most prevalent cancer in children, accounting for 25–30% of pediatric malignancies. Despite significant advancements in treatment leading to survival rates exceeding 90% for acute lymphoblastic leukemia (ALL) and 75% for acute myeloid leukemia (AML) in developed countries, challenges persist, particularly in managing refractory and relapsed cases. This review highlights the critical role of genetic profiling in the diagnosis and treatment of pediatric leukemia, emphasizing its potential to guide personalized therapeutic strategies. The integration of next-generation sequencing has revolutionized our understanding of the genetic heterogeneity of leukemia, enabling the identification of actionable mutations that inform risk stratification and targeted therapies. Furthermore, novel treatment modalities, including immunotherapy and targeted agents, are emerging as promising options for improving outcomes in high-risk patients. However, the need for less toxic treatment regimens remains urgent, as survivors often face long-term health challenges. This review underscores the importance of ongoing research to develop innovative therapies that minimize toxicity while maximizing efficacy, ultimately aiming to provide the right treatment for each patient at the right time.

Keywords: Leukemia, children, targeted therapy, precision medicine, molecular approaches.

INTRODUCTION

Leukemia is the most common type of cancer in childhood, accounting for 25–30% of cancers in children and adolescents aged 0–18 years (National Cancer Institute SEER Cancer Stat Facts Annual Report to the Nation 2019, German Childhood Cancer Registry Annual Report 2018). Over the past decades, survival rates have steadily increased and now exceed 90% for acute lymphoblastic leukemia (ALL) and 75% for acute myeloid leukemia (AML) in developed countries [1]. This success has mainly been achieved through remarkable progress in antileukemic treatment, risk-directed therapy, randomized clinical trials performed by collaborative study groups, supportive care, second-line treatment, and advances in the knowledge of leukemic cell biology including genomic variations [2].

The achievement of improved cure rates and survival into adulthood for most children with leukemia necessitates reduction of acute and long-term toxicity to minimize reduced quality of life, long-term morbidity, and premature death without compromising survival. Yet, even nowadays, leukemia remains the leading cause of death from cancer in children and adolescents in many developed countries. Especially, outcome of refractory/relapsed (r/r) leukemia remains poor. Indeed, it becomes more and more difficult to achieve further improvement of survival. This is demonstrated by survival rates of ALL, which seemed to reach a plateau, and the constant non-response/relapse rates despite intensified first-line therapy in AML [3]. In addition, the treatment paradigm of even further intensification of traditional multiagent chemotherapy including stem cell transplantation that allowed long-term disease-free survival in childhood leukemia reaches the point of inflection at which as many children decease due to r/r leukemia—and thus chemoresistance—as well as treatment-related toxicity. This underscores the urgent need to identify more effective and less toxic first line and salvage regimens for these patients [4].

To this end, the ever-expanding knowledge on leukemia biology is vital in identifying novel therapeutic targets by disclosing the heterogeneity of childhood leukemia, by unveiling the molecular drivers and by

understanding the mechanisms of drug resistance. These developments may ultimately brake with the practice paradigms of "one-size-fits-all" therapy and guide the development of precision/personalized treatment including immunotherapy and targeted (genomic) therapy to offer the "right drug for the right patient at the right time" even in children [5]. As such, treatment of chronic myeloid leukemia (CML) with imatinib (targeting BCR-ABL) is a prime example for precision oncology [6].

In recent years, several novel subtypes of AML and ALL with various prognostic impact have been identified. These are mainly characterized by genetic alterations that perturb multiple key cellular pathways including hematopoietic development, signaling or proliferation, and epigenetic regulation. These alterations partly include actionable genes and may thus serve as therapeutic targets. This progress is chaperoned by a brisk pace in genomic and immunological drug development. To date, several new drugs that may target these alterations have been approved by the European Medicines Agency (EMA) or the United States Food and Drug Administration (US FDA) or are still under development. However, it is hard to keep up with these rapid achievements in busy daily routine [7].

The Role of Genetic Profiling in Pediatric Leukemia Diagnosis:

The role of genetic profiling in the diagnosis of pediatric leukemia has become increasingly pivotal as advancements in genomic medicine have transformed our understanding of the disease's molecular underpinnings. Pediatric leukemia, particularly acute lymphoblastic leukemia and acute myeloid leukemia, is characterized by significant genetic heterogeneity, necessitating precise diagnostic approaches to tailor treatment effectively [8]. Genetic profiling enables clinicians to identify specific mutations and chromosomal abnormalities that are crucial for risk stratification and the selection of targeted therapies. For instance, performing genetic somatic sequencing panels for pediatric cancers has been shown to significantly impact clinical care in approximately 78.7% of pediatric patients, highlighting its importance in guiding treatment decisions and improving outcomes [9].

The application of next-generation sequencing has revolutionized the molecular characterization of pediatric leukemia. By utilizing targeted panels, researchers have identified recurrent structural alterations and age-specific mutational interactions in pediatric acute myeloid leukemia, which can inform prognosis and treatment strategies. Furthermore, the identification of specific genetic markers, such as RUNX1 mutations and deletions, has been associated with poor prognosis in pediatric acute myeloid leukemia, underscoring the necessity of genetic profiling for risk stratification. This stratification is essential, as it allows for the differentiation between high-risk and standard-risk patients, significantly influencing treatment intensity and the likelihood of relapse [10].

In addition to identifying mutations, genetic profiling also aids in understanding the immunophenotypic characteristics of leukemic cells. For example, the expression of specific antigens has been shown to correlate with the presence of acute leukemias, providing a rationale for the use of targeted immunotherapies. Moreover, the evaluation of cell surface markers can enhance the categorization of pediatric leukemia into risk groups, further refining treatment approaches. This comprehensive profiling not only facilitates the identification of therapeutic targets but also helps in monitoring minimal residual disease, which is critical for assessing treatment response and guiding subsequent therapeutic decisions [11].

The integration of genetic profiling into clinical practice has also led to the development of precision medicine approaches in pediatric leukemia. By leveraging the genetic information obtained from profiling, clinicians can implement targeted therapies that specifically address the molecular abnormalities present in a patient's leukemia. For instance, the use of tyrosine kinase inhibitors in Philadelphia chromosome-positive acute lymphoblastic leukemia exemplifies how targeted therapies can improve treatment outcomes by directly targeting the genetic alterations driving the disease. Furthermore, the identification of epigenetic modifications and their role in leukemogenesis has opened new avenues for therapeutic intervention, highlighting the importance of a multifaceted approach to treatment [12].

As research continues to elucidate the complexities of pediatric leukemia, the role of genetic profiling will only expand. The ongoing development of novel diagnostic tools promises to enhance the resolution of genetic alterations detected in leukemic cells, thereby improving diagnostic accuracy and treatment personalization. Additionally, the exploration of intratumoral heterogeneity through single-cell sequencing techniques may provide deeper insights into the clonal evolution of leukemia, which is crucial for understanding treatment resistance and relapse mechanisms [13].

Current treatment modalities:

Current treatment modalities for pediatric leukemia have evolved significantly over the past few decades, incorporating advancements in chemotherapy, targeted therapies, and immunotherapy. The two most common types of pediatric leukemia are acute lymphoblastic leukemia and acute myeloid leukemia, each requiring distinct treatment approaches tailored to their unique biological characteristics and patient-specific factors [14]. The standard treatment for acute lymphoblastic leukemia typically involves a multi-phase chemotherapy regimen, which includes induction,

consolidation, and maintenance phases. The goal of this intensive treatment is to achieve complete remission and prevent relapse, which is critical given that acute lymphoblastic leukemia accounts for approximately 80% of pediatric leukemia cases. Recent studies have demonstrated that the incorporation of asparaginase in post-remission therapy significantly improves outcomes, with randomized trials indicating superior event-free survival rates among patients receiving intensive asparaginase compared to those who do not [15].

In contrast, pediatric acute myeloid leukemia, which represents about 15-20% of pediatric leukemias, often requires more aggressive treatment due to its inherent biological aggressiveness. The treatment typically involves high-dose chemotherapy followed by consolidation therapy, which may include stem cell transplantation for high-risk patients. The prognosis for pediatric acute myeloid leukemia has improved with the use of risk stratification based on cytogenetic and molecular features, allowing for more personalized treatment approaches. For instance, patients with favorable cytogenetic profiles may receive less intensive therapy, while those with high-risk features, such as FLT3 mutations, may benefit from targeted therapies like FLT3 inhibitors [16].

Immunotherapy has emerged as a transformative approach in the treatment of pediatric leukemia, particularly for relapsed or refractory cases. Chimeric antigen receptor T-cell therapy has shown remarkable efficacy in treating relapsed B-cell acute lymphoblastic leukemia, with studies reporting complete remission rates of approximately 80% in this patient population. The success of chimeric antigen receptor T-cell therapy underscores the importance of genetic profiling in identifying suitable candidates for this innovative treatment modality. Moreover, bispecific T-cell engagers have also demonstrated significant activity in relapsed acute lymphoblastic leukemia, providing additional options for patients who may not respond to conventional therapies [17].

The integration of precision medicine into the treatment of pediatric leukemia has further enhanced therapeutic outcomes. Genetic profiling allows for the identification of specific mutations and alterations that can be targeted with novel therapies. For example, the development of siRNA-loaded lipid nanoparticles targeting long non-coding RNA has shown promise in preclinical models of pediatric acute myeloid leukemia, representing a novel therapeutic strategy that could be translated into clinical practice. Additionally, the use of proteomic profiling has been explored to identify potential biomarkers that could guide treatment decisions and improve patient stratification [18].

Despite the advancements in treatment modalities, challenges remain in managing the toxicities associated with intensive chemotherapy and the long-term effects of treatment. Survivors of pediatric leukemia often face significant health challenges, including metabolic syndrome and secondary malignancies, necessitating ongoing surveillance and supportive care. As such, the development of less toxic treatment regimens, including the use of nanotechnology for targeted drug delivery, is an area of active research aimed at minimizing adverse effects while maximizing therapeutic efficacy [19].

Other Targeted Approaches

Targeting Metabolic Enzymes

Two isoforms of isocitrate dehydrogenase (IDH), *IDH1* and *IDH2*, are among the most commonly mutated genes in AML occurring in about 20% of all newly diagnosed patients. They are key enzymes in the metabolism of a cell and also function in the regulation of oxidative stress. The heterozygous, mutually exclusive mutations occur at hotspot positions ($IDH1^{R132}$, $IDH2^{R140}$, $IDH2^{R172}$) and lead to a neomorphic enzyme activity resulting in the generation of very high levels of 2-hydroxyglutarate. This oncometabolite causes epigenetic changes and impairs cell differentiation. Preclinical data indicated early on that targeted inhibition of both IDH1 and IDH2 blocked colony formation of AML cells from *IDH1*-mutated patients and induced differentiation [20].

As there is great excitement regarding this class of inhibitors, many studies testing these substances both as monotherapies as well as in addition to standard chemotherapy backbones are being conducted, however, not yet in a pediatric setting, where *IDH1/2* mutations are rare.

Cell Cycle Regulation

Loss of cell cycle control resulting in unrestrained growth is generally considered a hallmark of cancer and aberrations in the cyclin-dependent kinase-retinoblastoma (CDK-Rb) pathway are common in multiple malignancies. Consequently, inhibition of this pathway is an attractive therapeutic strategy. The G1 cyclin-dependent kinases 4 and 6 (CDK4 and 6) phosphorylate—in a complex with cyclin D—retinoblastoma protein (Rb), which leads to cell cycle progression and cell growth [21].

More than 10 years ago, it was reported that the D-cyclin-CDK4/6 complex was a downstream effector of FLT3-ITD signaling. Inhibiting CDK4/6 caused sustained cell-cycle arrest . Another study showed that the CDK4/CDK6 kinase inhibitor palbociclib (PD 0332991) sensitized AML cells to cytarabine, opening the possibility of a combination therapy [22].

Ribociclib, another CDK4/CDK6 kinase inhibitor, enhanced glucocorticoid sensitivity in primary cultures derived from bone marrow of pediatric B-precursor ALL patients. A recent study showed that

palbociclib suppressed dissemination of Ph+ ALL and prolonged survival in a xenograft model [23].

Of special interest in the pediatric setting was the observation, that the KMT2A fusion proteins activate CDK6, thus driving proliferation in *KMT2A*-rearranged infant ALL. Treating *KMT2A*-rearranged leukemia cell lines with palbociclib resulted in a G1 arrest in ALL [24].

The various CDK4/6 inhibitors show similar side effects including high-grade hematologic toxicities, gastrointestinal and hepatobiliary toxicities, and QTc prolongation.

PARP Inhibitors

Several mechanisms seem to be responsible for the action of poly (ADP-ribose) polymerase (PARP) inhibitors, one is synthetic lethality. The PARP inhibitor blocks base excision repair leading to a double strand break. As tumor cells frequently have defects in homologous repair genes—such as *BRCA1*, *BRCA2*, *ATM*, or Fanconi anemia pathway mutations (which on their own are advantageous and result in growth advantages through increased genomic instability)—it will be unable to repair the double strand defect and will undergo apoptosis [25]. This makes the concept of PARP inhibitors attractive, as they target cancer cells based on their genetic deficiencies while sparing normal cells, which have backup mechanisms for repairing DNA strand breaks.

Preclinical evidence of the potency of PARP inhibitors in leukemia included anti-proliferative effects in T-ALL cell lines and re-sensitizing adriamycin-resistant leukemia cells. Recently, it was hypothesized, that *TET2*, which is frequently mutated in hematologic malignancies, maintains genomic stability via promotion of DNA damage repair and that loss of *TET2* might sensitize myeloid leukemia cells to PARP inhibitors [26].

As mentioned above, FLT3-ITDs, which can be found in up to 23% of AML patients, confer a poor prognosis. It was shown that treatment with a FLT3 inhibitor caused downregulation of DNA repair proteins. The combination with a PARP inhibitor significantly delayed disease onset and reduced leukemia-initiating cells in a FLT3-ITD-positive primary AML xenograft mouse model [27].

Many PARP inhibitors have been developed, of which two (olaparib and veliparib) have been tested in acute leukemias. A previous trial reported that veliparib/temozolomide was well tolerated and showed activity in advanced AML [28]. Several current trials are exploring PARP inhibitors, however only in the adult setting.

mTOR Inhibitors

The PI3K/Akt/mTOR pathway is a key regulatory pathway, which controls cell growth, survival, and cellular metabolism. The discovery of high mutational frequencies in multiple malignancies of both genes in the pathway itself but also in upstream, membrane-associated genes, early on sparked interest in targeting this pathway therapeutically. Upon mutation, this pathway becomes constitutively active in several malignancies, including ALL and AML. In some solid malignancies such as breast cancer and renal cell carcinoma, mTOR inhibitors are already firmly established in therapeutic regimens [29].

Early studies in leukemia showed that allosteric mTOR inhibitors resulted in decreased growth and induced apoptosis in ALL cell lines as well as xenograft models [30]. Mammalian target of rapamycin (mTOR) exists in two complexes, mTORC1 and mTORC2. The rapamycin analogs (rapalogs) everolimus, temsirolimus and sirolimus, which target mTORC1 through binding to the protein FKBP12 [31], were the first mTOR inhibitors to enter clinical trials.

Key Genetic Mutations and Their Implications for Personalized Treatment:

Among the most notable mutations are those involving the Mixed-Lineage Leukemia gene, which is frequently associated with aggressive forms of leukemia, particularly in children. The Mixed-Lineage Leukemia gene is often involved in chromosomal translocations, leading to the formation of fusion proteins that disrupt normal hematopoiesis and promote leukemogenesis. For instance, the MLL-AF4 and MLL-AF9 fusions have been shown to activate distinct signaling pathways that contribute to the malignancy of acute lymphoblastic leukemia and acute myeloid leukemia. Targeting the degradation pathways of these fusion proteins has emerged as a potential therapeutic strategy, highlighting the importance of understanding the underlying genetic alterations in developing effective treatments [32].

Another critical mutation in pediatric leukemia is the FLT3 (Fms-like tyrosine kinase 3) mutation, particularly the internal tandem duplication (FLT3-ITD). This mutation is prevalent in a subset of pediatric acute myeloid leukemia patients and is associated with poor prognosis due to its role in promoting cell proliferation and survival. The development of FLT3 inhibitors has provided a targeted treatment option for patients harboring this mutation. Clinical trials have demonstrated that these inhibitors can improve outcomes in high-risk patients, emphasizing the need for genetic testing to identify suitable candidates for such therapies. The identification of FLT3 mutations not only aids in risk stratification but also informs treatment decisions, allowing for a more personalized approach to therapy [33].

In addition to Mixed-Lineage Leukemia and FLT3 mutations, other genetic alterations such as NPM1 (nucleophosmin 1) mutations and CEBPA (CCAAT/enhancer-binding protein alpha) mutations have been implicated in pediatric acute myeloid leukemia. NPM1 mutations are associated with a favorable prognosis when present without FLT3-ITD, while CEBPA mutations can indicate a better response to treatment. Understanding these genetic profiles allows clinicians to tailor treatment regimens based on the specific mutations present in a patient's leukemia, thereby optimizing therapeutic outcomes [34].

The advent of next-generation sequencing technologies has revolutionized the landscape of pediatric leukemia by enabling comprehensive genomic profiling. This approach allows for the identification of actionable mutations that can be targeted with specific therapies. For example, the identification of mutations in genes such as TP53 and RUNX1 can indicate a higher risk of treatment failure and relapse, guiding clinicians in selecting more aggressive treatment strategies or experimental therapies. Furthermore, the integration of genomic data into clinical practice has facilitated the development of precision medicine approaches, where therapies are tailored based on the unique genetic makeup of each patient's leukemia [35].

Immunotherapy has also emerged as a promising treatment modality for pediatric leukemia, particularly in cases of relapsed or refractory disease. Chimeric antigen receptor T-cell therapy targeting CD19 has shown remarkable efficacy in treating B-cell acute lymphoblastic leukemia, with studies reporting complete remission rates as high as 82%. However, the emergence of CD19-negative leukemic clones poses a challenge, underscoring the need for continuous monitoring of genetic changes during treatment. The ability to adapt treatment strategies based on genetic profiling can enhance the effectiveness of immunotherapies and reduce the risk of relapse [36].

CONCLUSION

In conclusion, the landscape of pediatric leukemia treatment has undergone significant transformation over the past few decades, driven by advancements in our understanding of the disease's genetic and molecular underpinnings. The integration of genetic profiling into clinical practice has emerged as a cornerstone of personalized medicine, enabling clinicians to tailor treatment strategies based on the unique genetic alterations present in each patient's leukemia. This approach not only enhances the precision of risk stratification but also facilitates the identification of targeted therapies that can improve outcomes, particularly for high-risk patients. Despite the remarkable progress in survival rates for acute lymphoblastic leukemia and acute myeloid leukemia, challenges remain, particularly in managing refractory and relapsed cases. The need for innovative treatment modalities that minimize toxicity while maximizing efficacy is more pressing than ever. Emerging therapies, including immunotherapy and targeted agents, hold promise for addressing these challenges, but their successful implementation requires ongoing research and clinical trials to validate their effectiveness in pediatric populations.

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