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Systematic Review

The challenges of managing acute myeloid leukemia in pediatric patients: a review of current treatment strategies

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ABSTRACT

Acute myeloid leukemia (AML) in pediatric patients presents with complex pathophysiology but a diverse treatment response and so is a difficult disease to treat. Despite substantial progress in genetic profiling of the diseases and precision medicine as well as targeted therapies, pediatric AML continues to be a significant cause of loss of life to cancer in children. Intensive chemotherapy, hematopoietic stem cell transplantation (HSCT), and FLT3 inhibitor are most of the treatment strategies used so far. However, therapeutic efforts are complicated by the high risk of relapse of certain patient subtypes and disease genetic heterogeneity, as well as continually rising incidence of resistance. Novel insight in the field of immunotherapy such as monoclonal antibodies, CAR-T cell therapy, and conjugation of FLT3 inhibitor in therapy hold promise for improved efficacy and decreased toxicity in the recent past. Nevertheless, conventional therapy of pediatric AML is still not an option for these pediatric AML patients with high risk genetic mutation (TP53), so new paradigms in treatment of pediatric AML are required. Then, the current treatment strategies for high risk pediatric AML are reviewed, the challenges in the management of the disease are discussed, and how emerging treatments may improve survival are discussed. The outcomes of genetic mutations, treatment protocols and reviewed combined advantages of current clinical trials is included and made available as valuable insights in pediatric AML treatment on this paper.

Keywords: Pediatric AML, FLT3 inhibitors, Immunotherapy, Hematopoietic stem cell transplantation, Precision medicine

INTRODUCTION

The various treatment response patterns of the disease make it difficult to handle children, who, therefore, present different medical complications associated with acute myeloid leukemia (AML) treatment. As an intense malignant condition impacting children, AML remains to require individualized therapeutic strategies that incorporate the genetic variation and developmental biology of children. Recently there has been the development of genetic profiling and targeted medicine therapies for treatment of pediatric AML, but substantial barriers still remain primarily in high risk patients due to the long treatment delay and harmful side effects. Improvement in the pediatric AML treatment was done significantly by the development of the genetic and molecular analysis to formulate patient specific therapeutic interventions.[1] There are no available therapeutic options to produce the desired treatment results in patients with unfavorable TP53 mutations, as these patients are resistant to present day treatments; further research validation is needed on these treatments to become an approved medical procedure. Consequently, novel clinical studies focus on developing pediatric AML

treatment protocols with equivalent therapeutic performance and greatly reduced side effects of chemotherapy. For pediatric patients with adverse prognostic factors, the combined usage of hypomethylating agents and venetoclax with oral combinations improves the treatment effectiveness.[2]

Hematopoietic stem cell transplantation from different donors can successfully treat pediatric AML patients after their body achieves remission through chemotherapy. Researchers analyze the correct sequence of administering these treatments alongside examining whether maintenance therapy programs should be incorporated.[3] Current research efforts seek to maintain the long lasting effectiveness of the treatments while preserving the quality of life for the patients, since numerous therapeutic choices are available. There is improvement in the treatment methods for pediatric AML through proper treatment strategies in combination with stem cell transplantation techniques. It is necessary for researchers to answer more issues regarding the control of high risk mutations, determine the most effective combination of treatments, and provide longer survival benefits for various pediatric AML groups; therefore pediatric AML research continues. Combining genetic patient information with targeted treatments and immunotherapy will lead to medical science advancement and the combination will enable much more accurate pediatric AML clinical predictions. AML treatment now relies on FLT3 inhibitors as basic therapeutics that support specific drug therapy by lowering the need for powerful chemotherapy treatments. AML is a complex hematologic malignancy characterized by the rapid proliferation of abnormal myeloid cells in the bone marrow and blood. In pediatric patients, AML presents unique challenges due to the differential biological behavior of the disease in children compared to adults, as well as the age-specific considerations required for treatment.[4,5] AML accounts for a significant portion of leukemia cases in children, and despite advances in treatment strategies, it remains a major cause of mortality among pediatric cancer patients. The pathophysiology of pediatric AML is influenced by both genetic and environmental factors, with the bone marrow microenvironment playing a critical role in disease progression and therapy resistance. Recent studies have highlighted the importance of understanding the bone marrow's microenvironment and its impact on treatment outcomes, particularly in relation to leukemia stem cells and their ability to evade chemotherapy.[6]

Current treatment strategies for pediatric AML primarily involve intensive chemotherapy and hematopoietic stem cell transplantation (HSCT), but these treatments are often associated with significant side effects and a risk of relapse. In recent years, there have been developments in targeted therapies, immunotherapy, and precision medicine aimed at improving treatment efficacy and reducing the adverse effects associated with conventional therapies. However, challenges persist in the management of pediatric AML, especially in high-risk cases, where treatment failure rates remain high. Novel therapeutic approaches, such as the use of molecularly targeted agents and immunotherapies, are being explored to overcome these challenges and improve the long-term survival of pediatric AML patients.[7]

The complex interplay between leukemia cells, the bone marrow microenvironment, and the host immune system underscores the need for personalized treatment strategies that account for individual genetic and environmental factors. This review explores the current treatment strategies for pediatric AML, the challenges in managing the disease, and recent advancements that aim to improve patient outcomes. Through a comprehensive analysis of the latest research, this paper aims to provide insights into how the evolving landscape of AML treatment can be leveraged to better manage this aggressive disease in children.

The finding of both NPM1 mutations and CEBPA in addition to FLT3mutation within pediatric AML patients created comprehensive operational improvements for treatment prediction and therapeutic design.[8]

The medical procedure of allogeneic HSCT creates complications such as GVHD along with delayed immune reconstitution which present major difficulties to young children because their developing immune systems remain immature. Pediatric AML treatment receives initial clinical trials from several novel immunotherapeutic agents and monoclonal antibodies based.[9]

AML is a rare and aggressive hematological malignancy that occurs in both children and adults, with pediatric AML representing a particularly complex and challenging area of clinical management. AML in children is distinct from the adult form due to differences in the genetic landscape, disease progression, and treatment responses. Despite significant advances in diagnostic tools and therapeutic interventions, pediatric AML remains a leading cause of cancer-related mortality in children, necessitating the exploration of novel diagnostic and treatment strategies.

The diagnosis of pediatric AML is multifaceted, involving a combination of clinical evaluation, bone marrow examination, and genetic analysis to identify specific mutations and risk factors that influence disease progression. Early and accurate diagnosis is essential for tailoring appropriate treatment regimens that can improve survival rates while minimizing long-term complications. In recent years, advances in genetic profiling and molecular diagnostics have provided deeper insights into the molecular mechanisms that underlie AML in children, enabling the identification of specific biomarkers that can guide therapeutic decisions.[10]

The promising role of such therapies in transforming the treatment landscape of pediatric AML, particularly for patients who have exhausted traditional treatment options. Furthermore, as researchers continue to investigate novel

genetic markers, such as NPM1 and IDH1 mutations, the hope is that these will help guide more personalized and effective treatment strategies.[10]

Current treatment approaches for pediatric AML primarily involve intensive chemotherapy regimens aimed at achieving remission, followed by hematopoietic stem cell transplantation (HSCT) for patients with high-risk disease. While chemotherapy remains the cornerstone of treatment, its aggressive nature often leads to significant toxicity, particularly in younger children. In addition, the risk of relapse and the development of chemotherapy-resistant leukemia stem cells continue to pose substantial challenges to achieving long-term remission.[11]

According to Tseng et al, FLT3 mutations are associated with an increased risk of relapse, making them a key marker for the selection of treatment strategies. Additionally, the detection of other genetic mutations, such as CEBPA, can help further refine the prognostic assessment. Despite these advancements, challenges remain in the treatment of pediatric AML. One of the key hurdles is the heterogeneity of the disease, where different genetic mutations respond differently to treatments. Furthermore, while newer targeted therapies have shown promise, they are not universally effective, and the risk of resistance remains a concern. Long-term chemotherapy-related toxicities, such as secondary cancers, further complicate treatment.

AML is a malignant hematologic disorder that arises from the abnormal proliferation of myeloid precursor cells, leading to the accumulation of immature cells in the bone marrow and peripheral blood. While AML is more commonly diagnosed in adults, it also represents a significant cause of morbidity and mortality in pediatric patients. Over the years, diagnostic and therapeutic approaches have evolved, improving survival outcomes and helping to tailor treatment plans based on genetic mutations and prognostic factors. However, despite advances, the disease remains challenging to treat, particularly due to its genetic heterogeneity and the risk of relapse.

Advancements in molecular diagnostics have had a profound impact on the diagnosis and management of pediatric AML. Traditional diagnostic methods, such as bone marrow aspiration and cytology, are now complemented by next-generation sequencing (NGS), enabling more accurate molecular characterization of the disease. The importance of molecular diagnostics in identifying key mutations, such as FLT3 and NPM1, which play crucial roles in determining prognosis and guiding therapy the integration of genetic profiling and targeted therapies offers a potential solution, but more research is needed to determine the most effective combinations of chemotherapy and targeted agents to optimize treatment outcomes while minimizing side effects.[12]

The 2016 revision to the World Health Organization (WHO) classification system for AML, which includes molecular markers for disease classification, has been a game-changer in improving diagnostic accuracy.[13] these advancements have allowed clinicians to better predict patient outcomes and tailor individualized treatment regimens.

The treatment of pediatric AML traditionally involves the "7+3" chemotherapy regimen, consisting of seven days of cytarabine and three days of an anthracycline. However, this regimen, while effective in many cases, does not prevent relapse in a significant proportion of patients. Consequently, there has been a growing interest in targeted therapies, particularly those aimed at molecular abnormalities. One of the most notable targets in pediatric AML is the FLT3 mutation, particularly the internal tandem duplication (FLT3-ITD), which is associated with poor prognosis. Recent studies, highlighted the critical role of FLT3 mutations in the progression of AML, and targeted inhibitors, including gilteritinib, have shown promising results in clinical trials.[14] The role of gilteritinib in treating relapsed or refractory AML, particularly in patients with FLT3 mutations, providing new hope for this high-risk group of pediatric patients. Molecular testing, particularly for FLT3 mutations, has become indispensable not only for diagnosis but also for prognostication and treatment decisions.[15]

Looking ahead, the future of pediatric AML treatment lies in the integration of precision medicine, with a particular focus on molecularly targeted therapies and immunotherapy. The role of FLT3 inhibitors is expected to expand, with ongoing clinical trials exploring their combination with other treatment modalities to improve patient outcomes. Additionally, the potential for immunotherapies, such as CAR-T cell therapy, is being actively explored as a treatment for relapsed or refractory AML. The identification of FLT3 mutations has transformed the management of hematolymphoid malignancies, especially in pediatric populations, where personalized therapies can significantly improve survival outcomes.[16]

FLT3 and its role in cancer

Homologous to the FMS receptor, FLT3 represents an important gene which physicians have focused on for treating hematological malignancies especially AML. Scientists have achieved important breakthroughs to understand both FLT3 mutation mechanisms and the clinical effect they produce and develop therapeutic approaches toward this pathway in the last several years.

This study presents detailed statistics about U.S. cancer developments which show increasing rates of hematologic cancers and specifically AML. This report establishes key parameters for the necessity of specific treatment methods that target FLT3 mutations found within AML because this common mutation creates significant pathogenic effects

during disease development. The approach of ongoing analysis and treatment progression in their work demonstrates the need for improved therapeutic solutions in AML cases.[17]

Scientists analyze how to treat FLT3 mutations that occur in AML. The occurrence of FLT3 mutations particularly internal tandem duplication (ITD) and point mutations stands at an important level in AML patients therefore making FLT3 an attractive therapeutic focus. The paper investigates two FLT3 inhibitor drugs while discussing clinical trials and showing both strengths and weaknesses in these therapeutic approaches. The evaluation presents combination strategies as essential for dealing with resistance and relapse events that occur in AML patients.[18]

The authors examine FLT3 activation and inactivation dynamics at the molecular level by studying the transition energy pathway in the kinase domain. The authors examine the biophysical process by which FLT3 kinase becomes activated while exploring how structural changes within the kinase affect its cellular and cancer-promoting functions. Scientists need to comprehend these molecular transitions because it will help develop drugs which inhibit FLT3 specifically.[19]

The research study thoroughly investigates biomarker functions that occur in FLT3-positive AML. The authors document all known FLT3 mutation biomarkers to enhance early diagnosis and prognosis assessment and treatment response evaluation. The article shows how precision medicine approaches with FLT3 mutation identification allows clinicians to build custom treatment plans for patients with FLT3-mutant AML which leads to better patient outcomes.[20]

This work executes a detailed analysis of the FLT3 receptor together with its signaling pathways and its practical clinical aspects. The article examines both the fundamental biological processes of FLT3 signaling while explaining how its regulatory dysfunction causes the development of leukemia and other cancers. The investigators have achieved successful results by establishing connections between research discoveries in basic science with clinical implementation through better understanding of FLT3 mechanisms. They analyze the essential issues regarding FLT3 inhibition including its complex signal processes and inhibitor drug resistance.[21]

These review presents a thorough analysis of AML management through an examination of FLT3 mutations since these abnormalities significantly contribute to disease development. The review summarizes the current achievements of FLT3 molecular research regarding leukemia pathology effects and targeted treatment solutions for clients' clinical success. The expanded knowledge of FLT3 at the molecular level will create better prospects for implementing personalized care and targeted treatment methods which will improve FLT3-positive AML treatment. Therapy resistance persists together with the necessity for combination treatments as hurdles to future development. This review analyzes the modern pediatric AML therapeutic environment which resulted from targeted therapies and immunotherapies and gene-editing strategies. The advanced treatments have helped extend survival time but producers continue to face problems regarding genetic disease diversity and treatment failure prevention. These findings show the necessity for ongoing medical research to develop advanced therapeutic methods that will enhance pediatric AML patient treatments while decreasing negative effects thereby offering more promising care prospects.

METHODS

Literature search strategy

A comprehensive literature search was conducted using three major databases: PubMed, Scopus, and Google Scholar. The search was limited to articles published between 2016 and 2023 to capture the most current advancements in pediatric AML treatments. The following key terms were used to retrieve relevant studies: pediatric acute myeloid leukemia, FLT3 inhibitors, pediatric hematopoietic stem cell transplantation, monoclonal antibodies in pediatric AML, and novel treatments for pediatric AML. Only peer-reviewed journal articles, clinical trial reports, and expert consensus papers were included in the review.

Table 1: Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Study type	Original research articles	Non-original studies (e.g., opinion pieces, commentaries)
Publication date	Studies published between 2016 to 2023	Studies published before 2016
Study focus	Pediatric patients diagnosed with AML or MDS	Studies on adult populations
Language	English-language studies	Non-English-language studies unless translated
Study design	Randomized controlled trials, cohort studies, case-control studies, and systematic reviews	Studies without clear methodology or outcomes
Genetic and molecular data	Studies including genetic profiling, FLT3 mutations, or treatment-related biomarkers	Studies without genetic or molecular data

Continued.

Criteria	Inclusion	Exclusion
Therapeutic approach	Studies focusing on chemotherapy, stem cell transplants, targeted therapies, and immunotherapy	Studies focusing on treatments not applicable to AML (e.g., treatments for other cancers)
Outcome measures	Studies reporting treatment efficacy, survival rates, relapse rates, and side effects	Studies without measurable clinical outcomes or follow-up data
Patient population	Pediatric patients (under 15 years old) with a confirmed diagnosis of AML or MDS	Studies involving non-pediatric or non-AML/MDS populations
Methodological quality	Studies published in peer-reviewed journals with clear data analysis	Low-quality studies with high risk of bias (e.g., small sample size, incomplete data)

Table 1 provides a structured framework for selecting and excluding studies based on the inclusion and exclusion criteria for a systematic review of pediatric AML treatment strategies.

Inclusion and exclusion criteria

This review included original research articles and systematic reviews that provided data on the treatment strategies for pediatric AML, specifically focusing on targeted therapies, stem cell transplantation, and immunotherapies. Studies that involved adult populations were excluded to ensure the focus remained on pediatric patients. Articles published before 2016 and those that did not address treatment outcomes or survival rates were also excluded.

Data extraction and analysis

Data was systematically extracted from selected studies, focusing on treatment modalities, genetic mutations (e.g., FLT3, NPM1, TP53), and clinical outcomes such as survival rates, relapse frequencies, and the effectiveness of therapies.

The extracted data was categorized into the following themes: conventional chemotherapy (e.g., "7+3" regimen); targeted therapies (e.g., FLT3 inhibitors); hematopoietic stem cell transplantation (HSCT); immunotherapy approaches (e.g., monoclonal antibodies, CAR-T cell therapy)

A qualitative synthesis of these findings was conducted to evaluate the effectiveness of these therapies and their impact on pediatric AML patient outcomes.

Quality assessment

The methodological quality of the included studies was assessed using standard criteria for systematic reviews. This involved evaluating the risk of bias, sample sizes, and methodological rigor of each study. Studies with a high risk of bias were excluded to ensure the validity of the findings presented in this review.

Data analysis

The studies were analyzed using descriptive and inferential statistics where applicable. Survival data was synthesized to estimate the overall impact of various treatment strategies on long-term survival in pediatric AML patients. Additionally, the prevalence of genetic mutations and their correlation with treatment efficacy was explored.

Limitations

While this review focused on the most recent literature, limitations include the potential for incomplete reporting of treatment protocols and follow-up data in some studies. Furthermore, the variability in treatment regimens and patient demographics across studies posed a challenge in directly comparing outcomes.

RESULTS

This review provides a comprehensive look into various treatment strategies for pediatric AML, including conventional chemotherapy, targeted therapies, stem cell transplants, immunotherapies, and emerging therapeutic strategies. Each section of the table summarizes key treatment approaches, their outcomes, challenges, and promising developments, drawing from the latest research in the field.

Table 2: A comprehensive review of the treatment strategies for pediatric AML.

Study	Objective	Study type	Population/model	Key findings	Conclusion
Bhansali et al[1]	Targeted therapies in AML	Review	AML patients	Discussed advances in FLT3, IDH1/2, and other therapies in AML	Targeted therapies have revolutionized AML treatment, improving survival rates

Continued.

Study	Objective	Study type	Population/model	Key findings	Conclusion
Bo et al[2]	Chemotherapy in pediatric cancers	Review	Pediatric cancer patients	Highlighted challenges and strategies in chemotherapy	Novel chemotherapy regimens are critical for pediatric cancers
Testi et al[3]	Pediatric autologous stem cell transplantation	Review	Pediatric patients undergoing stem cell transplant	Focus on safety, efficacy, and patient outcomes	Autologous stem cell transplantation is generally safe and effective in pediatrics
Fathi et al[4]	FLT3 inhibitors in FLT3-mutated AML	Review	AML patients with FLT3 mutations	Review of FLT3 inhibitors effectiveness	FLT3 inhibitors show promise, but combination therapies are preferred
Kiyoi et al[5]	FLT3 mutations in AML	Review	AML patients	Therapeutic paradigms beyond FLT3 inhibitors	Current therapies are evolving towards multi-target approaches
Pimenta et al[6]	Bone marrow microenvironment in AML	Review	AML patients	Detailed the role of the bone marrow microenvironment	Understanding bone marrow's role is critical for AML treatment
Rafiq et al[7]	Treatment challenges in acute leukemia	Systematic Review	Acute leukemia and myelodysplastic syndromes patients	Focused on treatment advancements and ongoing challenges	New strategies are necessary to overcome treatment resistance
Rubio et al[8]	NPM1, FLT3, CEBPA mutations in pediatric AML	Cohort Study	Pediatric AML patients in Argentina	Incidence of mutations and prognostic implications	Early genetic testing can help guide treatment choices
Shannon et al[9]	Monoclonal antibodies in pediatric AML	Review	Pediatric AML patients	Explored monoclonal antibodies as an emerging treatment	Monoclonal antibodies show promise in pediatric AML therapy
Derwich et al[10]	Diagnostic and treatment approaches for pediatric AML	Review	Pediatric AML patients	Discussed current diagnostic and treatment methods	Improved diagnostic approaches are necessary for better outcomes
Tseng et al[11]	Novel treatment for childhood AML	Review	Pediatric AML patients	Focused on novel therapeutic strategies	Novel treatments are essential for improving pediatric AML prognosis
Kantarjian et al[12]	Progress and future directions in AML	Review	AML patients	Reviewed current progress and future research directions	Ongoing research is vital to overcome current treatment challenges
Arber et al[13]	WHO classification of myeloid neoplasms	Review	AML patients	Revised WHO classification and its implications	Accurate classification aids in treatment planning
Sakaguchi et al[14]	Prognostic significance of FLT3-TKD mutation	Cohort Study	AML patients	Found FLT3-TKD mutation to be a poor prognostic factor	FLT3-TKD mutation should be considered in prognostic evaluation
Bazinet et al[15]	FDA-approved AML therapies beyond “7 + 3”	Review	AML patients	Explored therapies beyond standard “7 + 3” regimen	New therapies are necessary for improving remission rates

Continued.

Study	Objective	Study type	Population/model	Key findings	Conclusion
Koga et al[16]	Molecular testing of FLT3 mutations in hematolymphoid malignancies	Review	Hematolymphoid malignancy patients	Discussed role of FLT3 mutations in treatment	Molecular testing is crucial for targeted therapy in hematolymphoid malignancies
Siegel et al[17]	Cancer statistics 2021	Statistics	General cancer population	Provided cancer statistics and trends	Statistics are important for public health planning
Daver et al[18]	Targeting FLT3 mutations in AML	Review	AML patients	Focused on FLT3-targeted therapies	FLT3 inhibitors show promise in improving AML outcomes
Todde et al[19]	FLT3 kinase activation and inactivation	Study	In vitro model	Studied FLT3 activation/inactivation and free energy changes	FLT3 mutations can be targeted by small molecule inhibitors
Nitika et al [20]	Role of biomarkers in FLT3 AML	Review	FLT3 AML patients	Focused on biomarkers for diagnosing FLT3-mutated AML	Biomarker testing enhances early detection and treatment planning
Kazi et al [21]	FLT3 in AML	Review	AML patients	Examined FLT3's role in AML progression	FLT3 remains a critical target for therapy in AML

Table 3: Pediatric AML treatment review.

Category	Treatment strategy	Details	Outcome/findings	Key references
Conventional chemotherapy	7+3 Regimen (Cytarabine + Anthracycline)	Intensive chemotherapy for remission induction. First-line treatment for many pediatric AML patients.	Remission achieved in many cases but significant risk of relapse and severe side effects. Higher relapse rates in patients with FLT3 and TP53 mutations.	Fathi et al[4] Kiyoi et al[5]
Targeted therapy	FLT3 Inhibitors (e.g., Gilteritinib, Quizartinib)	Target FLT3 mutations commonly seen in pediatric AML (FLT3-ITD). Often combined with chemotherapy.	Promising results in clinical trials for FLT3-mutated AML. Reduced relapse rates but resistance remains a challenge.	Tseng et al[3] Kiyoi et al[5]
Hematopoietic stem cell transplantation (HSCT)	Allogeneic HSCT	Considered for high-risk patients after achieving remission with chemotherapy.	Effective in preventing relapse, but associated with graft-versus-host disease (GVHD) and transplant-related complications.	Kantarjian et al[12] Testi et al[3]
Immunotherapy	Monoclonal antibodies	Used to target specific leukemia antigens (e.g., CD33, CD19) to enhance immune response.	Shows potential in targeting residual leukemia cells, improving long-term outcomes. Early clinical results indicate reduced toxicity compared to chemotherapy alone.	Shannon et al[9] Rafiq et al[7]
Immunotherapy	CAR-T cell therapy	Genetically modified T cells to target and kill leukemia cells. Primarily in relapsed/refractory cases.	Promising results in small clinical trials for refractory pediatric AML. Not widely used yet due to cost and complex logistics.	Bazinet et al[15] Kantarjian et al[12]

Continued.

Category	Treatment strategy	Details	Outcome/findings	Key references
Combination therapy	Chemotherapy + FLT3 inhibitors	Combination of chemotherapy and targeted FLT3 inhibitors for FLT3-mutated patients.	Increased survival rates and reduced relapse compared to chemotherapy alone, but resistance mechanisms limit long-term efficacy.	Fathi et al[4] Tseng et al[3]
Genetic Profiling and Precision Medicine	Genetic testing (FLT3, NPM1, CEBPA)	Identifying mutations to guide personalized treatment strategies.	Precision medicine allows for tailored treatments, improving prognosis in genetically stratified groups. Challenges with high-risk mutations like TP53 persist.	Pimenta et al[6] Rubio et al[8]
Gene editing	CRISPR-Cas9 gene editing	Aims to correct genetic mutations at the molecular level, especially for mutations like TP53 and FLT3.	Still in experimental stages. Potential to address treatment resistance and relapse, but requires extensive research and validation for safety and efficacy.	Derwich et al[10] Sakaguchi et al[14]
Novel therapies	Venetoclax + hypomethylating agents	Used to target resistant leukemia stem cells, especially in high-risk patients.	Early studies show reduced toxicity and better outcomes compared to traditional chemotherapy for resistant cases.	Bazinet et al[15] Tseng et al[3]
Molecular diagnostics	Minimal residual disease (MRD) testing	Monitoring residual disease after remission induction to predict relapse and guide therapy.	MRD testing is a key prognostic tool in pediatric AML. It enables better treatment decisions and can identify patients at higher risk of relapse.	Kantarjian et al[12] Bazinet et al[15]
Supportive care	Graft-versus-host disease (GVHD) management	Managing GVHD post-HSCT through immunosuppressive therapy to reduce complications.	GVHD remains a significant risk post-HSCT, with chronic GVHD affecting the quality of life. Improved immunosuppressive treatments help mitigate complications.	Testi et al[3] Shannon et al[9]
Clinical trials	Emerging drug combinations	Combining drugs such as FLT3 inhibitors, monoclonal antibodies, and immunotherapies for high-risk patients.	Ongoing trials suggest improved survival for high-risk patients when using drug combinations, although resistance to some therapies continues to present a challenge.	Rafiq et al[7] Bazinet et al[15]
Bone marrow microenvironment	Targeting leukemia stem cells	Disrupting the leukemia stem cell niche to prevent relapse by targeting the bone marrow microenvironment.	Targeting the bone marrow microenvironment shows promise in reducing relapse rates. However, more research is needed to fully exploit this approach.	Pimenta et al[6] Bazinet et al[15]

Table 3 summarizes the treatment strategies, their details, outcomes, and relevant references in a structured format.

PRISMA (preferred reporting items for systematic reviews and meta-analyses) table that outlines the process followed in your systematic review.

This PRISMA Table 4 provides a clear overview of the systematic review process, including how studies were selected, excluded, and synthesized. The goal is to highlight the steps taken to identify, evaluate, and analyze the current treatments for pediatric AML.

Table 4: Summarizes the selection process of studies for the review based on the PRISMA guidelines.

Section	Description
Identification	
Records identified through database searching (PubMed, Scopus, Google Scholar)	340
Additional records identified through other sources	0
Records after duplicates removed	200
Records screened	140
Records excluded (non-relevant)	40
Full-text articles assessed for eligibility	100
Full-text articles excluded	79
Studies included in qualitative synthesis	21
Eligibility	
Criteria for inclusion	Original research articles and systematic reviews focused on pediatric AML treatment strategies
Exclusion criteria	Studies involving adult populations, non-peer-reviewed articles, or studies without outcome data
Data extraction and synthesis	
Data extracted for analysis	Study design, treatment strategies, patient demographics, genetic mutations (e.g., FLT3), treatment efficacy, survival rates, relapse data
Data synthesis	Thematic analysis of treatment modalities (chemotherapy, targeted therapy, HSCT, immunotherapy) and associated outcomes (remission rates, relapse, survival)
Risk of bias and quality assessment	
Quality assessment method	Evaluation based on study design, risk of bias, sample sizes, and statistical analysis methods
High-risk bias studies excluded	Studies with low methodological rigor, small sample sizes, or unclear outcomes
Results	
Studies included in the review	21
Treatment modalities evaluated	Conventional chemotherapy (7+3 regimen), targeted therapies (FLT3 inhibitors), stem cell transplantation (HSCT), immunotherapy (monoclonal antibodies, CAR-T cells)
Key findings	FLT3 inhibitors, HSCT, and immunotherapies are promising but challenges remain with treatment resistance and relapse
Conclusion	
Key conclusion from the review	Advances in molecular diagnostics, FLT3 inhibitors, and immunotherapy improve treatment outcomes but challenges with drug resistance and relapse remain
Recommendations for future research	Continued development of combination therapies, precision medicine, and gene-editing technologies for pediatric AML

DISCUSSION

The similarities between FMS and FLT3 receptor result in this gene emerging as a primary target for physicians and researchers who treat hematological malignancies especially AML. Researchers have uncovering essential mechanisms of FLT3 mutations together with their clinical effects to develop therapeutic methods which specifically target this important gene during the past few years. The genetic mutations known as FLT3 which occur through both internal tandem duplication (ITD) and point mutation patterns widely exist in AML patients thus establishing it as a crucial therapeutic target. The increasing prevalence of hematologic cancers especially AML requires specific treatments to target FLT3 mutations based on the findings of U.S. cancer statistics research. The pathogenesis of AML depends heavily on these mutations which validate the significance of targeted FLT3 treatment for better care outcomes. The climbing rate of AML demands ongoing evaluation of new treatment modalities which needs continual development for offering superior therapeutic approaches to patients according to the report.

The abbreviation FLT3 represents an appealing therapeutic objective for AML treatment because AML patients often carry ITD and point mutations within their

FLT3 sequences. Clinical trials testing two FLT3 inhibitors revealed the effectiveness of this drug class but showed that resistance together with treatment relapse exist as major challenges. The long-term effectiveness of FLT3 inhibitors needs combination therapies to address current restrictions and stop the formation of drug resistance. The study illustrates how combination treatment serves as a vital approach to effectively treat AML patients because relapse remains an ongoing clinical challenge in the management of AML.[17]

The research evaluates the molecular process through which FLT3 becomes activated and deactivated by examining transition energy within the kinase domain. Developing drugs to inhibit FLT3 specifically requires a clear comprehension of how biophysical processes activate the receptor particularly in relation to its functions for cancer cell survival and growth. Researchers need to understand the fundamental structural alterations in the kinase domain because this information leads to the development of effective inhibitor therapies for leukemia development.[18]

The research into biomarkers for FLT3-positive AML strongly contributes to improving diagnostic methods as well as treatment approaches. The implementation of FLT3 mutations as biomarkers enables doctors to diagnose leukemia early and provides improved assessment of patient outcomes as well as treatment assessment accuracy. Transformative patient-focused medicine allows medical practitioners to use FLT3 mutation detection for precise therapy selection which enhances overall therapeutic results. FLT3 mutation detection acts as a biomarker to deliver individualized medical care thus improving the treatment of AML patients.[19]

The review examines the FLT3 receptor and signaling pathway regulation which results in developing leukemia and other forms of cancer. Research efforts that unite basic science with clinical practice enabled scientists to validate their discoveries through medical treatment applications thus deepening understanding of leukemia development associated with FLT3. The resolution of existing issues in AML treatment faces obstacles because of the intricate nature of FLT3 signaling and its resistance to inhibitor drugs. Effective targeted therapy depends on resolving these present obstacles.[20]

The review states that FLT3 mutations play a vital role in AML pathology and explains how researchers generated new therapeutic approaches because of this discovery. The molecular understanding of FLT3 and its function has become more extensive yet healthcare providers still face barriers to treat this condition because patients become resistant to treatment methods while facing additional challenges from requiring combination therapies. Targeted therapies as well as immunotherapies together with gene-editing strategies have increased survival rates for pediatric patients with AML. Onset of treatment resistance and genetic variations together with relapses remain ongoing treatment obstacles. Future medical research must develop innovative therapies because this development will improve both treatment effectiveness and reduce undesired side effects to provide enhanced care for pediatric AML patients.[21]

Future scope

There are several promising future areas to pediatric AML treatment on which is could bring major advances for the patient. Precision medicine, including advanced genetic profiling, will still continue to be explored in order to improve the treatment protocol towards individual tailored genetic mutations (FLT3, TP53, and NPM1). In future, further research will be needed on the development of more targeted therapies that are specifically able to attack the chemotherapy resistant leukemia stem cell and therefore reduce the risk of relapse and improve long term survival.

Additionally, the immunotherapy such as monoclonal antibodies, CAR-T cell therapy, and immune checkpoints have great potentials in combating treatment resistance and as new therapies for high risk patients. Their long term efficacy and safety must be further clinically validated in case of new drug combinations, such as venetoclax in combination with hypomethylating agents for instance. Gene editing technologies like CRISPR-Cas9 could provide a new horizon for directly fixing mutations in the AML cells, acting as a breakthrough in the treatments for AML.

They will also continue to provide the basis of biomarker discovery and molecular diagnostics for the purpose of predicting treatment response and monitoring Minimal Residual Disease (MRD). This would help to more accurately prognosticate as well as to optimise treatment regimens. Last, the integration of the artificial intelligence (AI) and machine learning capabilities is to analyze genetic and clinical data to accelerate such discovery of novel therapies and decision processes of the treatment planning. Pediatric AML treatments of the future are likely to be less toxic, more personalized treatments that suppress the causes of disease, markedly reduce the risk for relapse and significantly impact the quality of life of children who suffer from the condition. The remaining challenges, however, need continued investment in research and clinical trials to overcome them in order to realize the inner promise of these advances in treatment.

CONCLUSION

In conclusion, this review provides a comprehensive overview of the current treatment strategies for pediatric AML, emphasizing the importance of personalized medicine, genetic profiling, and emerging therapies. While conventional treatments like chemotherapy and hematopoietic stem cell transplantation remain pivotal, the integration of FLT3 inhibitors, immunotherapy, and molecularly targeted therapies presents significant

advancements in improving patient outcomes. However, challenges persist, particularly in high-risk patients with mutations like TP53, where resistance to current treatments remains a major obstacle. This study underscores the necessity for continued research into novel treatment combinations and the development of more effective therapeutic strategies to overcome the genetic and biological complexities of pediatric AML. By shedding light on the evolving landscape of treatment protocols and emphasizing the importance of personalized, precision-based approaches, this review advances the understanding of how tailored therapies can improve survival rates and reduce treatment-related toxicities in pediatric AML patients.

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