2025
12(2), 1262

Chemical Biology
LETTERS

Updated insights on clinical diagnosis and targeted therapy of acute myeloid leukaemia (AML): A molecular approach

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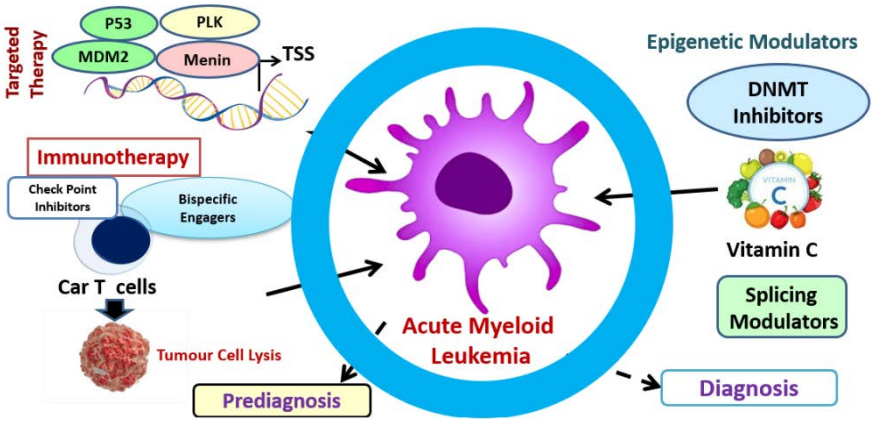
Submitted on: 12-Jun-2024, Accepted and Published on: 18-Nov-2024

Review

ABSTRACT Acute myeloid leukaemia (AML) is the most common acute leukaemia in adults, with around 20,000 annual diagnoses in developing countries. Its pathogenesis involves genetic mutations, such as NPM1, CEBPA, and FLT3-ITD, alongside chromosomal translocations that lead to the proliferation of poorly differentiated myeloid cells. While AML is a primary concern, it is essential to consider other leukaemia types and associated risk factors. Prognosis in AML varies among patients with similar cytogenetic profiles, categorized as favorable, intermediate, or adverse. Standard treatments include chemotherapy regimens, such as anthracycline and cytarabine, and allogeneic stem cell transplantation. Recent research highlights the significance of mutations in signal transduction pathways and transcription factors in myeloid differentiation. Continued exploration of these genetic factors will enhance our understanding of AML and improve treatment outcomes, emphasizing the need for a comprehensive approach to patient management. Finally, AML genetic research and clinical consequences may improve treatment regimens and patient outcomes.



Keywords: *Acute myeloid leukaemia, Stem cell therapy, Cytogenetics, Myeloid sarcoma*

INTRODUCTION

Most frequent kind of acute leukaemia, making up around 80% of adult cases, is acute myeloid leukaemia (AML). Acute lymphoblastic leukemia (ALL) is defined as the metastatic transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood, and extramedullary areas. In the US, three to five AML cases are recorded for every 100,000 individuals. In 2015, the illness claimed the lives of almost 10,000 people, and 20,830 new cases were estimated.[1,2] Even though 80% of cases of ALL are in youngsters, the illness can be fatal in adults. The incidence of AML increases with age, with patients over 65 experiencing a surge in instances from around 1.3 per 100,000 to 12.2 per 100,000. With advances in AML therapy, the prognosis for younger individuals has improved dramatically, but for older patients, who account for most new cases, it remains poor.[3] Although adolescent patients' results have significantly improved as a result of dose-intensification procedures, the prognosis for geriatric patients is still quite dismal.[4] Recent developments in our understanding of the molecular etiology of AML have been driven by the identification of key genetic mutations and characteristic cytogenetic abnormalities. Studies have demonstrated that these chromosomal alterations often result in fusion genes that disrupt the function of transcription factors crucial for myeloid development, highlighting AML as a disorder of dysregulated transcriptional control. This progress has been made feasible by the cloning of relevant genes and the first description of characteristic cytogenetic changes more than ten years ago. Studies subsequently showed that most chromosomal

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URN:NBN:sciencein.cbl.2025.v12.1262
DOI:10.62110/sciencein.cbl.2025.v12.1262

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abnormalities characteristic of AML give rise to fusion genes containing transcription factors essential for myeloid development, and that the resulting fusion proteins impair the function of these transcription factors.[5] These results support the idea that AML is a disorder of dysregulated transcriptional control. Notably, tyrosine kinase receptor mutations, particularly in the FLT3 gene, have been implicated in AML pathogenesis, underscoring the potential for more individualized treatment approaches based on specific clinical and molecular characteristics. While data on targeted therapies remain limited, a growing body of research emphasizes the role of frequent mutations in signal transduction pathways, such as Ras, in AML development. In blasts of AML, tyrosine kinase receptor-activating mutations have been discovered more recently; these alterations mainly affect Flt3. Our emphasis on FLT3-mutated AML supports the capacity to further individualize treatment based on clinical factors in addition to cytogenetic or molecular features, even if there are a few data accessible on the web with limits in targeted therapy. This has led to a paradigm change by emphasizing earlier research on frequent mutations in other signal transduction mediators, such as Ras, and linking impaired signal transduction to the development of AML to some extent.[6] This review aims to synthesize recent findings in the molecular biology of AML, with a focus on how these insights can inform more effective, personalized therapeutic strategies for patients.

METHOD

Search strategy

A systematic review of the literature from 1996 to 2024 was conducted using the Scopus, Google Scholar and PubMed databases, as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analysis criteria. The search included phrases such as 'Acute myeloid leukaemia,' 'Stem cell treatment,' 'Cytogenetics,' 'Myeloid sarcoma,' and 'MAPK pathway,' 'JAK kinases,' 'Chemotherapy,' and development of different hematopoietic lineages molecular targeted therapy'. There were no limitations in the search strategy.

Scope of the review

This paper examines several aspects of acute myeloid leukaemia, including its pathophysiology and classification according to the World Health Organization (WHO), molecular cytogenetics, biobanking, diagnostic tests, and treatment modalities such as chemotherapy, targeted therapy, central nervous system therapy, and molecular specific therapy. With the exception of the aforementioned procedures, there were other therapeutic techniques that met the exclusion criteria. The exclusion criteria included both duplicate research and articles authored by the same individual that were identical. We excluded review papers and other publications that did not provide comprehensive information on innovative or updated therapies. After conducting a separate evaluation of the titles and abstracts, the authors used inclusion and exclusion criteria. A comprehensive collection of relevant research materials was obtained. Further papers were selected after reviewing the references to the retrieved articles. Discussion and reaching a consensus helped the reviewers resolve their disagreement.

Data extraction and outcome

Upon first search, a total of 1156 items were listed. An exploration of relevant citations within the references of the first study yielded an additional 76 scholarly articles. A total of 1232 records were discovered. After a systematic evaluation of titles and abstracts, a total of 341 publications were selected for further analysis. Following a thorough assessment of the entire material, 163 items in total were disqualified using the standards given in the methods section. There are 178 investigations in all in the final qualitative synthesis.

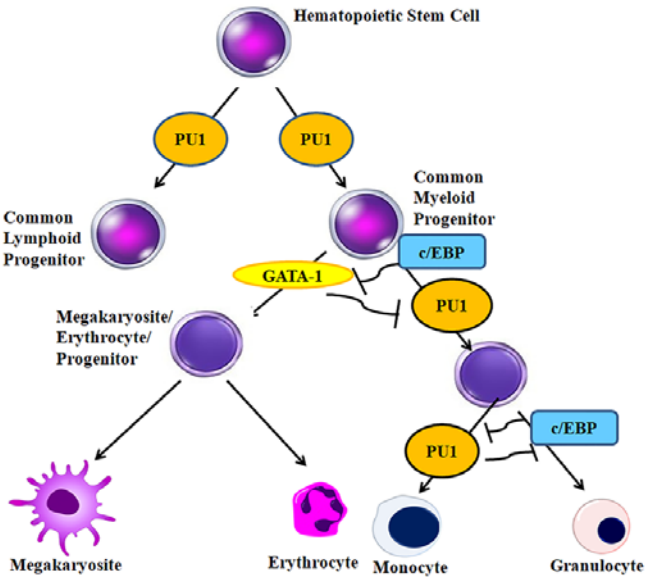

Figure 1. The role of transcription factors and their interplay in the development of different hematopoietic lineages.

PATHOPHYSIOLOGY AND WHO CLASSIFICATION

A clonal population of lymphoid cells that proliferates and differentiates abnormally is part of the pathophysiology of ALL (Figure 1). Some children with genetic disorders such as Bloom syndrome, Down syndrome, ataxia telangiectasia, Fanconi anaemia, and Nijmegen breakdown syndrome have an increased risk of developing ALL, but these instances are rare.[7] Additional risk factors include being infected with viruses like Epstein-Barr and human immunodeficiency virus (HIV), using pesticides, using certain solvents, and being exposed to ionizing radiation.[8-10] But in the majority of cases, it manifests as a de novo cancer in previously healthy patients. Even while chromosomal abnormalities are the hallmark of ALL, they cannot be the exclusive cause of leukemia. Rearranging MLL and the translocations t(12;21) [ETV6-RUNX1], t(1;19) [TCF3-PBX1], and t(9;22) [BCR-ABL1] are examples of characteristic translocations.[11-13] This suggests that kinase inhibitors may be useful in treating Ph-like ALL, which frequently has a worse prognosis, which has significant therapeutic implications.[14,15] As many as 50% of AML patients have increased tyrosine phosphorylation of STAT3, which is suggestive of a poorer prognosis. This may be due to increased production of cytokines such as IL-6, modifications to receptor tyrosine kinases such as JAK2, or, less frequently, FLT3 duplications.[16] Prominent class II

mutations linked to improved prognoses include NPM1 (discovered in 27% of patients) and CEBPA (found in 6% of patients), respectively.[7] A third category of mutations has been discovered recently: those connected to epigenetic regulation. A third category of mutations has been discovered recently: those connected to epigenetic regulation. Cell differentiation and proliferation are impacted by these changes. Based on the "two-hit model," the way different chromosomal rearrangements and somatic alterations interact has a major impact on how AML forms and behaves. Consequently, the c-KIT mutation has been identified by the medical departments at the New York University School of Medicine in New York, NY, USA, as well as the departments of Haematology and Oncology at the New York University Perlmutter Cancer Centre in New York, NY, USA. The department of Haematology/Oncology at NYU School of Medicine may be found at 240 East 38th Street, 19th floor, New York, NY 10016, USA. This is the Perimutter Cancer Center in New York. The Blood Cancer Journal states that t(8;21) or inversion is associated with and has a major impact on prognosis. An increase of malignant, poorly differentiated myeloid cells in the bone marrow, peripheral blood, and perhaps other organs is the primary cause of most clinical symptoms associated with AML. The majority exhibit leukemia, thrombocytopenia, and anemia as symptoms of bone marrow depletion. Less often occurring symptoms include organomegaly and lymphoma; anorexia, exhaustion, and weight loss are typical. If bleeding or infections are not treated for months after diagnosis, they typically result in death. Acute leukemia is diagnosed when 20% or more blasts are seen in the peripheral blood or bone marrow.[17]

Classification

The first attempt to differentiate between various forms of antimony laundering was made using the classification system created by the Americans, British, and French. The eight subtypes (M0 to M7) of leukemic cells differ in their morphology and cytochemical properties. In 1976, this classification scheme was created. The World Health Organization (WHO) unveiled a revised classification system in 2001 in an effort to reflect developments in the identification and management of AML. An improved version was released in 2008.[18] The WHO revised its classification of AML later in 2016, defining six main disease categories that include morphology, immunophenotype, clinical presentation, and genetic information: AML not otherwise described, therapy-related AML, AML that has recurrent genetic abnormalities, AML that is related to myelodysplasia, myeloid sarcoma, and myeloid.

Signal transduction

Once RTK, or cytokine receptors, are activated, several intricately connected intracellular signaling cascades that alter the expression of genes and protein modifications that are essential for cell survival and proliferation are nearly always triggered (Figure 2). These signaling cascades are similar to pathways, as shown by historical biochemical and genetic data. This occurs as a result of some signaling intermediates being "downstream" of other cascade participants. Among the earliest pathways to be discovered, the Ras-MAPK pathway modifies transcription in the nucleus by activating RTKs. It involves many intermediate steps that activate the small GTPase Ras.[19-22] GTP-bound Ras initiates a cascade of serine/threonine and dual specificity kinases, which in turn activate the MAPK family of mitogen-activated protein kinases.[23-28] Some kinases cause the target cell to divide by phosphorylating crucial transcriptional regulators of cell cycle progression.[29] Recent focus has also been directed on the PI3-Kinase/Akt pathway, another signaling mechanism. Indirect routes connecting Src-family kinases and activated kinases may initiate this process indirectly, or directly, by binding and phosphorylating a PI3-Kinase regulatory subunit to an active RTK.[30,31] In mammals, PI3-Kinase is responsible for producing a tiny lipid secondary messenger that activates a number of serin/threonine kinases, including Akt and mTOR, the target of rapamycin. These proteins directly influence the translation process, which controls the growth and development of cells. They also play a part in regulating apoptosis and proliferation. To just a few, the STAT group of signaling intermediates is crucial.[32,33]

STAT3 and STAT5, which were initially discovered during the signal transduction of cytokine and interferon receptors, are essential for myeloid differentiation and survival. This is due to the fact that many cytokine receptors, such as the IL-3 receptor, activate them. Myeloid cells' cytoplasm contains constitutively expressed transcription factors. In order to generate signaling complexes, activated cytokine receptors interact to JAK kinases and receptor subunits.

In this case, phosphorylation of tyrosine residues results in dimerization and translocation of the proteins to the nucleus. Target gene transcription is started by STAT3 and STAT5, which are involved in the regulation of apoptosis and the advancement of the cell cycle. Although organizing our understanding of signal transduction's intermediates requires breaking the process down into routes, this nevertheless represents a significant simplification of the process. Their paths will cross several times. For instance, Ras may start the PI3-Kinase pathway directly.[34] When cytokine receptors are present, JAK-proteins, Src family members, and occasionally RTKs can also activate STAT proteins.[35,36] Further downstream, the locations of signal integration might be identified by observation. MAP-Kinases, for instance, are responsible for the modification of the transcriptional activity of STAT proteins by the addition of a phosphate group to certain serine residues.[37,38] Moreover, a number of strategies are used by the PI3-Kinase-Akt pathway and STAT proteins to raise the amounts of Bcl2 family members that prevent cell death.[33,39] Hematopoietic progenitor cells have a combination of growth factor receptors. Therefore, in addition to the signaling network's primary role of promoting survival and proliferation, it has been shown that certain growth factor receptors and signaling intermediates are necessary for myeloid differentiation. For instance, TPO- or G-CSFR-induced Ras-activation may activate GATA-1 and c/EBP, respectively, to promote myeloid or megakaryocytic growth in the pertinent progenitor cells.[40,41] It has been demonstrated that Flt3 induces the dual-functioning transcription factor Pu.1 to both express and activate. Pu.1 either stimulates monocytic or lymphoid development, depending on the level of its cellular expression; in some circumstances, it also induces monocytic differentiation in

the absence of other growth factors.[42-44] Understanding the complete pathophysiology of AML, including growth factor receptors that have been incorrectly activated and the related signaling intermediates in myeloid development, is therefore essential (Table 1). Determining the effects of signal transduction molecules on various cell kinds and stages is significantly more challenging than determining the overall effects of these molecules on survival and proliferation. Our sophisticated models will be necessary to deliver consistent outcomes. As will be discussed later, growth factor-activating mutations certain Flt3 mutations prevent myeloid differentiation by directly preventing the synthesis and activity of myeloid transcription factors.[45-47]

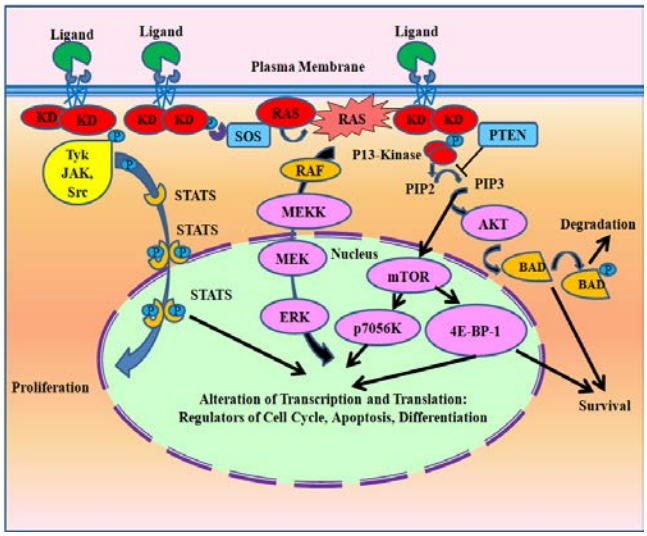

Figure 2. Schematic representation of some intracellular signaling pathways with relevance for the patience treatment of AML.

Table 1: Recent drugs approved by Food and Drug Administration (FDA) (since 2017) for acute myeloid leukaemia.

Treatment (approval date)	Description	Indication
Midostaurin (April 2017)	Multikinase FLT3 inhibitor	Newly diagnosed FLT3-mutated (as detected by FDA-approved test) AML, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Gemtuzumab ozogamycin (September 2017)	Anti-CD33 antibody–drug conjugate	Adults with newly diagnosed CD33-positive AML; refractory-relapsed CD33-positive AML in patients ≥ 2 years of age
CPX-351 (August 2017)	Liposomal cytarabine and daunorubicin at a fixed 5:1 molar ratio	Newly diagnosed therapy-related AML, secondary AML or AML with myelodysplasia-related changes
Glasdegib (November 2018)	Hedgehog pathway inhibitor	Newly diagnosed AML aged ≥ 75 years or with co-morbidities that preclude the use of intensive induction chemotherapy (in combination with low-dose cytarabine)
CC-486 (September 2020)	Oral azacitidine hypomethylating agent (30% absorption) approved at 300 mg daily × 14 every month	Continued treatment of adult patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and who are not able to complete intensive curative therapy
Oral Decitabine-cedazuridine (July 2020)	Oral hypomethylating agent (100% absorption)	Alternative to parenteral HMAs decitabine for the treatment of adults with MDS (pretreated/untreated; de novo/secondary) or CMML

Molecular cytogenetics

AML treatment needs a precise prognostic assessment. There are different types of treatments that doctors can use, such as standard or stepped-up treatments, allogenic hematopoietic stem cell transplantation, consolidation chemotherapy, and, most importantly, prognostic markers (Figure 3). Patients are categorized based on their likelihood of treatment resistance or treatment-related mortality (TRM). Poor performance status and increasing age are clinical variables associated with reduced rates of complete remission (CR) and decreased overall survival (OS).[3,48] The prediction of TRM risk is also influenced by age and performance level at diagnosis. Multivariate model analysis suggests that the majority of the observed greater risk of TRM may be better explained by other parameters, such as albumin, serum creatinine, or platelet count, than by age alone. T(8;21), t(15;17), chromosomal rearrangements with inversion, chromosomal rearrangements, and t(6;9)(p23;q34.1); inv(3)(q21.3q26.2), all offer favorable prognoses for MLLT3-KMT2A persons for patients under the age of sixty.[16,49] The 3-year OSs for these patients are 66% and 33%, respectively. There is a much higher chance of treatment not working or even death if you have monosomy 5 or 7, t(6;9), inv(3), or 11q changes other than t (9;11), or a complex karyotype, which means you have three or more chromosomal abnormalities but no other genetic abnormalities that were found in the WHO 2008 classification.[50,51] Most AML cases with an intermediate prognosis risk are patients with normal cytogenetics (CN-AML).[17,52] Although there are signs that individuals with inversion[16] have a comparable inferior prognosis owing to c-KIT mutations, the current investigation has not demonstrated any prognostic effect in this class of situations. Patients with intermediate-risk AML had nearly the same overall survival as those with c-KIT mutations.[53-55] About 50% of de novo AML cases are CN-AML patients, for whom molecular alterations are a key predictor of prognosis. Thus, prognosis risk for CN-AML without FLT3-ITD with a mutant CEBPA or modified NPM1 has been shown to be comparable to that of AML with advantageous cytogenetic abnormalities.[17,56] More information has been made available on the positive prognostic effect of biallelic mutations alone in CEBPA mutations. Nevertheless, there is a wealth of evidence linking FLT3-ITD to a worse prognosis.[57,59] One such study is a meta-analysis of overall survival (OS) and relapse-free survival (RFS) in CN-AML patients under 60 years of age.[6,60] Using CN-AML and FLT3-ITD. Biallelic variants have the same potential to impact FLT3-ITD prognosis as mutations in CEBPA. Numerous investigations have shown that patients with higher allelic ratios of mutants to wild-types had a noticeably poorer

prognosis. Only 2–8% of cases had TP53 mutations, albeit they are more common in those with complicated karyotypes and poor cytogenetics.[61-63] In contrast, mutations in the TP53 gene are linked to an extremely poor, and regardless of the cytogenetic profile, they may even constitute the most detrimental genetic risk factor.[63] DNA-related gene mutations significantly affect the treatment and prognosis of AML. The histone methyltransferase gene KMT2A (previously known as MLL) has partial tandem duplications that have been linked to a poorer prognosis.[63] It has been demonstrated that IDH-1/IDH-2 mutations enhance OS in patients with FLT3-ITD-negative and NPM1-mutant CN-AML. Six Nevertheless, no predicted correlation was seen between OS or treatment response in recent research with 826 people whose IDH-1 and IDH-2 status was known.[64,65] It will need further research to determine how DNA-related genes affect OS and the effectiveness of therapy. Apart from DNA profiling upon diagnosis, data collected post-therapy is progressively enhancing the prognosis of patients: Depending on whether or not their thrombocytopenia is cured, patients who achieve CR have varying survival times.[66,67] Lately, methods like as flow cytometry and real-time PCR have been employed to assess if patients in CR have low residual.

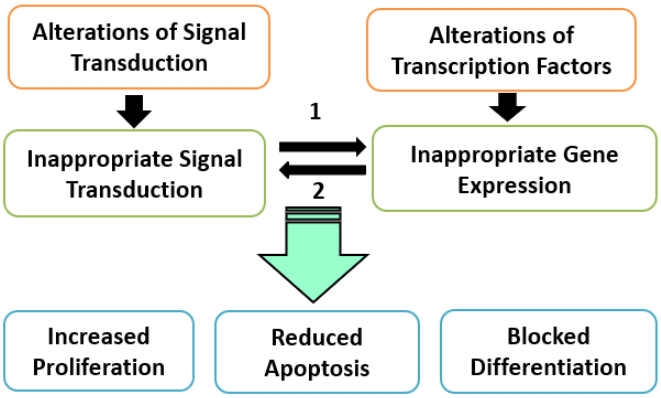

Figure 3. The interaction of many molecular changes in AML progression. While changes in transcription factors result in improper gene expression, changes in signal transduction mediators cause inappropriate signal transduction.

Biobanking

The idea of biobanks began as straightforward biological sample storage facilities and has developed into dynamic, sophisticated organizations that are a component of extensive infrastructure networks like the Pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI). The goal of biobanks is to increase scientific understanding. A diverse group of professionals from several disciplines collaborates to collect and acquire biological and clinical data from subjects. Each person's legal and human rights are upheld when biobanks provide biomaterial for research.[68]

The vast amount of data that is stored in today's biobanks may be used to identify biomarkers for certain illnesses. They do this by using well-annotated clinical and biological data in conjunction with digital or biological material (bioimages). Since the identification of relevant biomarkers is an essential initial step in the diagnosis and prognosis of disease, these qualities are required to enhance personalized medicine.[69]

The circumstances in which patients are informed and seek agreement to use their biological samples for research have been the subject of several studies in the area of cancer research.[6,7,20] These studies have taken this preference into consideration. While there are some overlaps, Axler et al. showed that decisions regarding biological cell or tissue donation (organs, blood, or bone marrow) for a specific therapeutic project are influenced by different factors than decisions regarding other forms of medical voluntarism. The authors also stressed the need of comprehending how a cancer diagnosis can alter the attitudes of prospective donors towards donation.[70] The reasons for and experiences of cancer patients who consented to be part of research by letting their samples be stored in biobanks, on the other hand, have not received much scrutiny. In a preliminary investigation, an uncommon occurrence was spontaneous concern regarding the handling and preservation of biological samples among breast cancer patients who had provided informed consent to donate blood or tissue samples for scientific objectives. For the families of children with cancer, the value of tissue donation lay more in its ability to bind the families to their childhood community than in its symbolic meaning of the self; consenting to participate in biobanking was regarded as a way to honour the medical care that the children had acquired and become a part of the earlier generations of research participants. This was because it anchored these families in their childhood neighbourhood rather than embodying the essence of each person. Patients and guardians who had kids who had contributed tumour tissue to biobanks were the subjects of a small-scale research carried out by Morrell et al. They noted that patients' attitudes towards the donation of tumour tissue for research are only partly explained by concepts of altruism and social exchange, and they highlighted the technique of revalorization of the tumour tissue that motivates the act of donation.[71]

Diagnostic tests

A comprehensive approach including several diagnostic techniques is necessary for the diagnosis of AML in order to confirm the disease's presence and identify its specific subtype. First, a complete blood count (CBC) is performed to evaluate the various components of the blood. This test often shows lower platelet counts (thrombocytopenia), decreased hemoglobin levels (anemia), and increased white blood cell counts (leukocytosis), all of which are signs of leukemia. A peripheral blood smear is examined under a microscope after the CBC. The presence of blast cells, which are immature cells suggestive of AML, and the identification of abnormal white blood cells are made easier by this evaluation. Additional context for the diagnosis is provided by evaluating the erythrocyte and thrombocyte morphology. A bone marrow aspiration and biopsy are often the last test used to diagnose AML. Usually from the iliac crest, a sample of bone marrow is taken. The percentage of blast cells in the sample is measured; a diagnosis of AML often requires a threshold of 20% or above. The biopsy provides insight into the bone marrow's structural integrity, which may be weakened in leukemia. After that, cytogenetic analysis looks for structural anomalies, such as

translocations, deletions, or inversions, in the chromosomes of leukemic cells. Since different variants correspond with distinct subtypes of AML and may have a significant impact on prognosis and treatment strategies, it is essential to identify specific chromosomal abnormalities. A precise technique that makes it possible to identify specific genetic mutations and chromosomal changes, including fusion genes, is fluorescence in situ hybridization (FISH). To get a more thorough genetic profile of the leukemic cells, this method is often combined with cytogenetic analysis. AML diagnosis and therapy increasingly depend on molecular testing. Certain gene changes, such as those in FLT3, NPM1, and CEBPA, are detected using techniques including polymerase chain reaction (PCR) and next-generation sequencing (NGS). Prognosis and treatment decisions may be significantly impacted by these mutations, particularly when using targeted medications. Using flow cytometry, immunophenotyping looks at leukemic cells' cell surface markers. In order to differentiate AML from other types of leukemia, such as acute lymphoblastic leukemia (ALL), and to classify the specific subtype of AML, which might inform treatment strategies, this test is crucial. A lymph node biopsy may be performed to check for the presence of leukemic cells outside the bone marrow when extramedullary disease is suspected. Although imaging tests like computed tomography (CT) scans may be used to assess how leukemia has spread to other organs or tissues, they are often ineffective in diagnosing AML. Since coagulopathy may appear in people with AML, coagulation tests may be part of further laboratory examinations to assess bleeding problems. Biochemical panels evaluate kidney and liver function, which are important considerations for designing a treatment. Blood tests, bone marrow analysis, cytogenetic and molecular research, and immunophenotyping are all used in the intricate process of diagnosing AML. This meticulous approach not only confirms the diagnosis but also provides crucial information about the nature of the illness, guiding customized treatment plans and improving patient outcomes overall. The diagnostic framework for AML is continuously being improved by advancements in molecular genetics and a better knowledge of the biology of the illness, allowing for more individualized and efficient treatment approaches.[70,71]

MANAGEMENT OF AML

The most prevalent form of acute leukaemia in adults is AML. Previously, if they had an HLA-matched family donor, fit young people with AML in the first CR (CR1) were eligible for treatment with allogeneic hematopoietic cell transplantation (HCT). Fit young individuals with AML in the first CR (CR1) were formerly eligible for therapy with allogeneic hematopoietic cell transplantation (HCT) provided they had an HLA-matched family donor. While the primary focus of this study will be on the management of younger patients, it should be acknowledged that older individuals may be even more eligible for an early transplant due to biologic issues. For the duration of their treatment, patients need to receive supportive care and acute management, but during the initial days to weeks of intensive induction therapy, this is especially crucial. As was previously indicated, although AYA are more likely than younger children receiving chemotherapy or HSCT to have TRM, they are also frequently able to tolerate more demanding regimens than older patients. AML treatment outcomes have improved recently, to the point that 56 studies now include hazardous and genotype-adapted therapy. This means that it is now even more important to balance treatment toxicity and intensity, as well as how these characteristics connect to the illness's genetic background. Compared to children, adolescents have greater anticipatory vomiting. When most chemotherapy is administered in a hospital, AYA, kids, and elderly patients all adhere to the strict treatment plans in a comparable manner throughout the course of the treatment. Teenagers receiving maintenance therapy for AML in nations like Germany might not take their medicine as prescribed, similar to how teens with ALL might not take their oral chemotherapy as prescribed. Providing psychological care to teens is the most challenging part of managing them. Adolescents have distinct demands than do little children. Basic aspirations for things like independence and autonomy, social growth, sexual maturity, education, and work are among these demands.[72]

These problems are similar to those faced by AYA with various cancer types. The European Society for Medical Oncology/European Society for Paediatric Oncology recently released survey findings that exposed the substantial disparities in and contempt for AYA cancer care throughout the continent. The study recommended concentrating research and educational efforts on enhancing adolescent and young adult cancer therapy.[73] Young adults are the age group in the US with the highest rates of under- and uninsurance. After leaving their parents' health care, about half of all teens between the ages of 15 and 19 do not have enough insurance.[72] To diagnose APL, one needs a high index of suspicion. For PML/RARA, a diagnosis must be made as soon as possible using RT-PCR and FISH, or as soon as possible using karyotype for t(15;17). Even when there is coagulopathy in addition to the normal immunophenotype and the shape is non-typical, one still needs to proceed with extreme care. For additional care, it is advised that all patients with this diagnosis be sent to a tertiary referral center. It is imperative that therapy begin as soon as a diagnosis is made. ATRA should be used as the first line of therapy as soon as a diagnosis is suspected. In addition, it is imperative that supportive therapy for coagulopathy be started as soon as possible.

TREATMENTS FOR AML

For newly diagnosed cases of AML, induction therapy is the first step of treatment. Remission induction treatment is another term for induction therapy. The two major goals of AML induction treatment are to achieve a full response, also known as a complete remission, and to rid the blood and bone marrow of leukaemia cells, also known as blast cells or blasts. Usually given over the course of a week, this therapy might keep you in the hospital for as long as five weeks as you wait for any adverse effects to go away and for the bone marrow to return to normal function. Based on your needs, our medical experts will work with you to develop a treatment strategy and will suggest induction

procedures. Usually, chemotherapy and targeted treatment are employed.[74]

AML is treated with a variety of important medications, each of which has a distinct chemical structure that influences how it works. A cytosine base joined to an arabinosyl sugar with a hydroxyl group at the 2' position is what makes cytarabine (Ara-C) a deoxycytidine pyrimidine analog. By integrating into DNA and impeding elongation, it prevents DNA synthesis. The complicated tetracyclic structure of the anthracycline antibiotic daunorubicin has an anthraquinone core connected to a sugar moiety called daunosamine. It creates free radicals that kill cells and intercalates into DNA, blocking transcription and replication. Idarubicin is an additional anthracycline that functions similarly to daunorubicin by inhibiting topoisomerase II and causing breaks in DNA strands. It has an altered sugar moiety and additional hydroxyl groups that increase its effectiveness. Although the synthetic anthracenedione mitoxantrone has structural similarities with anthracyclines, its distinct three-ring structure reduces cardiotoxicity. It causes apoptosis and DNA damage by intercalating into DNA and blocking topoisomerase II. With a nitrogen atom at the 5-position of the pyrimidine ring, azacitidine is a cytidine nucleoside analogue that acts as a DNA methyltransferase inhibitor to correct abnormal methylation and promote leukemic cell differentiation. Decitabine, a counterpart of deoxycytidine, reactivates suppressed genes linked to cell growth by blocking DNA methyltransferases. A humanized monoclonal antibody that targets CD33 is coupled to the cytotoxic substance calicheamicin to form gemtuzumab ozogamicin, an antibody-drug combination. This tailored approach causes selective cell apoptosis by delivering the cytotoxic chemical straight to leukemic cells that express CD33. Together, these medications are crucial for treating AML, and their unique chemical makeup greatly enhances their therapeutic effectiveness.[76,88]

Chemotherapy

Induction therapy is the initial course of treatment when acute myeloid leukemia (AML) is discovered. Another name for induction therapy is remission induction therapy. Eradication of leukemia cells, sometimes called blast cells or blasts, from the bone marrow and blood, and full response, also called complete remission, are the two main objectives of AML induction therapy.[75] This therapy, which is usually given over the course of a week, may necessitate up to five weeks in the hospital as you wait for any adverse effects to go away and for the bone marrow to resume normal function. Together, you and our medical staff will develop a treatment plan, and according on your requirements, our specialists will suggest induction therapies. Chemotherapy and targeted treatment are typically employed. When induction treatment yields a positive response, consolidation therapy should be started in order to completely remove any remaining illness and establish a durable remission.[76] The "7+3" regimen, which consists of an unbroken seven days of cytarabine infusion following three days of anthracycline, is the cornerstone of induction therapy. It is commonly used to treat younger patients who have minimal risk of TRM, an intermediate to positive prognosis, and adequate platelet counts, creatinine concentrations, and albumin levels.[77] Studies employing induction regimens with idarubicin at 12 mg/m^2 or daunorubicin at 60 or 90 mg/m^2 have demonstrated comparable rates of CR and survival. Compared to palliative chemotherapy and supportive care, induction treatment improves survival in patients over 65, despite the much worse prognosis.[78] It must thus be applied whenever it is practical. Hypomethylating medications were once used to treat myelodysplastic syndrome (MDS), but they have also shown promise in the management of older individuals with AML. In a 2012 randomized study, individuals 65 years of age or older were compared to see if low-dose cytarabine or supportive care worked better with the hypomethylating drug decitabine.[79] The primary analysis did not identify a statistically significant survival advantage. The experiment found that recipients of hypomethylating treatment had a significantly higher overall survival rate.[80] Azacitidine did not improve median overall survival (OS) in patients 65 or older compared to supportive care, low-dose cytarabine, or traditional induction chemotherapy.[81] On the other hand, subgroup analysis suggests that patients who were specifically chosen to receive supportive care would benefit from azacitidine medication. Patients with multidrug-resistant acute myeloid leukemia (MDR-AML) with cytogenetic risk profile negative showed similar advantages.[82] To assess the patient's response to induction treatment, a bone marrow sample and core biopsy should be carried out 14 days following the start of therapy.[17] After receiving induction therapy, 60–80% of de novo AML patients can achieve complete remission (CR) with mitoxantrone, etoposide, and/or cytarabine.[83] Relapsed patients need consolidation therapy to eliminate residual illness and prevent relapses. The two treatments for consolidation are chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT).[84] When choosing between these various regimens, take into account the risk of treatment failure or recurrence in addition to the risk of TRM. Allo-HSCT is not superior to chemotherapy for cytogenetically favorable AML in first CR, according to trials that allocate patients to treatment according on donor availability.[85]

Concerning the optimal consolidation treatment plan for individuals with favorable gene mutations but an intermediate-risk cytogenetic profile, this is the most contentious subject.[86] Transplantation does not appear to be beneficial for patients with FLT3-ITD-negative, NPM1-mutated CN-AML, according to several studies.[87] Nonetheless, there are signs that allo-HSCT improves retention-free survival (RFS) in this particular patient cohort, according to a recent intention-to-treat trial.[88] Contradictory results can be explained by differences in study designs or by the moderating effect of coexisting mutations (such IDH-1/-2.6) on results that are shown. However, given that allo-HSCT has been demonstrated to significantly improve overall survival (OS) and response-free survival (RFS) in most patients with adverse-risk AML and in certain individuals with intermediate risk, it should be regarded as the first consolidation therapy for those who qualify.[82,89] Prolonged RFS and improved OS have also been demonstrated with allo-HSCT in patients with CN-AML with a high allelic ratio of FLT3-ITD. Physicians have found success using FLT3-ITD, a TK receptor inhibitor, in

treating a range of solid and hematological malignancies, including leukemias with Philadelphia chromosome positivity.[90,91] It has long been known that because FLT3 mutations are quite prevalent and have an impact on prognosis, blocking this TK is crucial.[92,93] Single-agent sorafenib at dosages ranging from 200 to 400 mg twice daily produced complete response (CR) in more than 90% of cases in a phase II study including thirteen patients with r/r FLT3–ITD-positive AML.[94] Elevated transaminases (3 out of 13), diarrhea (4 out of 13), dermatitis (2 out of 13), pancreatitis (1 out of 13), colitis (1 out of 13), pericarditis (1 out of 13), hand and foot syndrome (2 out of 13), and high creatinine (1 out of 13) were among the adverse events that were categorized as grade 3 to 4. In overall, the agent was favorably received.[95] After a 72-day period of remission, most patients experienced a recurrence, even with a good initial response.[96] Therapy failure was linked to the presence of mutations D835Y and D835H within the FLT3 TKD. Even while early stages I and II studies of combination therapy provided longer disease-free survival, relapse often occurred a few months after treatment.[97] When sorafenib is added to normal induction regimens, inconsistent results have also been seen. In one study, sorafenib, cytarabine, and idarubicin as induction and consolidation therapy helped 18 FLT3-ITD-positive AML patients who had never been treated achieve CR or partial platelet recovery.[98] A nine-month follow-up revealed that more than half of these individuals had relapsed. It is important to highlight that there were no newly identified, genetically sequence able mutations in the FLT3 TKD of the relapsed samples.[99] Treatment failure has also been linked to various types of resistance, such as elevated FLT3 receptor ligand levels in recipients of traditional chemotherapy.[100] Although sorafenib and hypomethylating drugs are being studied in tandem, there is no proof that one causes the other's FLT3 receptor ligand levels to rise. The role of sorafenib in AML's first treatment: In a promising phase II study using sorafenib plus azacitidine, 43 patients with relapsed or refractory AML participated. According to the findings, there was a 46% response rate, with 16% CR and 27% CR with partial count recovery.[101] In a multicenter randomized controlled phase II study, 267 newly diagnosed AML patients aged 60 or younger were included. Rollig et al., completed the most recent research on the combination of sorafenib and conventional chemotherapy.[102] Patients were randomized to receive sorafenib (400 mg twice day) as consolidation therapy following two rounds of traditional "7+3" induction treatment or three cycles of high-dose cytarabine consolidation therapy. Patients in the sorafenib group received sorafenib maintenance medicine for an additional 12 months after their final consolidation round. The main goal was three-year event-free survival, which was accomplished by 20% of patients receiving a placebo and 40% of patients receiving sorafenib (uncorrected hazard ratio of 0.64). Since sorafenib targets FLT3 TK during the post-daunorubicin or cytarabine treatment period, it may show substantial anti-leukemic actions even in cells lacking FLT3-ITD. Surprisingly, FLT3 TK inhibition has also shown promise as a relapse prevention or maintenance treatment in the post-allo-HSCT setting. This is comparable to treating leukemias that are positive for the Philadelphia chromosome with TKI. Chen et al., reported that 22 FLT3-ITD-positive patients got sorafenib as maintenance therapy following allo-HSCT in phase I research.[103,104]

Particularly for the group of patients who were in CR1 or CR2 at the time of transplant, the PFS and OS rates reported by the trial's authors were better than those of historical controls. They also provided proof of viability and safety. Similar to sorafenib, midostaurin, a first-generation FLT3 TKI, has some good but erratic single-agent efficacy in AML patients. However, resistance grows fast, making it less effective than sorafenib. Recently released data from a phase I and combined phase I/II research employing midostaurin and azacitidine show that this combination is safe and beneficial for patients with AML.[105] Research is now being conducted on the interactions between midostaurin and existing chemotherapies. No toxicities with a dosage limit were observed. A phase I/II experiment looked at individuals with primary or secondary AML and MDS to see if azacitidine and midostaurin had any synergistic benefits.[106] Individuals who were randomized to the midostaurin treatment group were also administered midostaurin as a year-long maintenance drug. There was no difference in the incidence of CR between the midostaurin and placebo groups.[107] Nonetheless, people using midostaurin had a significant improvement in their OS and EFS (hazard ratios of 0.77 and 0.80, respectively).[108] Second-generation inhibitor quizartinib was developed specifically to target FLT3 kinase and lessen toxicity from off-target effects. Because of its strong half-life of over 24 hours, excellent absorption, and improved selectivity, quimartinib inhibits FLT3 for a longer amount of time. In a phase I study, 30% of patients with recurrent or refractory AML responded haematologically to oral quizartinib.[109] Thirty percent of patients experienced treatment-related tiredness, twenty experienced diarrhea, twenty experienced feverish neutropenia, and twenty had QT interval prolongation. In 38 cases, patients experienced nausea, and in 26 percent of cases, vomiting. In 28-day cycles, males were given 135 mg of the medication daily, while women were given 90 mg.

On the other hand, among patients who tested negative for FLT3-ITD, the composite CR (i.e., CR, CR with incomplete platelet recovery, and CR with incomplete haematological recovery) had a composite OS of 44% and a percentage of 23.1 months, respectively. The observed improvement may be explained by an activation of the FLT3 TK pathway or by off-target effects, as suggested by the rise in FLT3 receptor ligand levels in FLT3-ITD-negative disease. Once more, however, the rapid onset of resistance restricts the response to FLT3 TKI: the median duration of remission was just 5 weeks in AML patients positive for FLT3-ITD.[110] An interim analysis of a phase I/II study found that quizartinib with azacitidine or cytarabine in combination treated 82% of FLT3-ITD-positive AML, MDS, or chronic myelomonocytic leukaemia patients.[111] A phase III trial (NCT02039726) is another investigation looking at how well quizartinib alone works in patients with recurrent and refractory AML as compared to salvage chemotherapy. Clinolanib. An in-depth examination and 2016 update on cenolanib besylate, an oral

second-generation FLT3 TKI that targets FLT3-TKD and AML I M FLT3-ITD cells.[112]

Clonolanib seems to block a broad range of secondary TKD mutations. This is not the case with other FLT3 TKIs, such D835Y, which may cause kinase domain mutations that compromise the therapeutic efficacy of the medication. even at far lower concentrations than plasma levels that may be obtained for medicinal purposes. Smith et al. did not find a single TKD mutation that may confer resistance to crenolanib.[113] In 38 FLT3-mutated AML patients in a phase II study, crenolanib three times a day for 28 days produced a median OS of 19 weeks and an EFS of eight weeks. This included both those who had previously received therapy and those who had not reacted to it.[114] Clonolanib is now being studied in a number of clinical studies involving AML patients, both with and without FLT3-mutated AMLs. Recent research indicates that when exposed to the tailored chemical MM-206, AML cell lines grown with bone marrow stromal cells show a dose-dependent activation of apoptosis. MM-206 has been demonstrated to inhibit malignancies in vivo by reducing the number of blasts and prolonging the life duration of AML-afflicted mice.[115] A little medication called OPB-31121 has shown promise in the treatment of advanced solid cancers by inhibiting the phosphorylation of STAT3 and STAT5.[116] Many leukemic cell lines, including AML cells that were FLT3-ITD positive, were considerably restricted in their ability to proliferate by this substance.[117]

Notably, OPB-31121 prevented FLT3 receptor ligand-induced STAT3 phosphorylation, which may prevent resistance in FLT3-ITD TKI patients. More antisense oligonucleotides (ASOs) that target STAT3—STAT3 inhibitors—are being studied in clinical trials for hematological malignancies. A recent attempt has been made to directly target these altered enzymes in order to cure AML. Wang et al., (2013) reported the findings of AGI-6780, a modest pharmacologic inhibitor of the IDH-2 enzyme with a mutation of R140Q.[118] Giving primary human AML cells outside of the body AGI-6780 broke down the differentiation barrier of leukemic cells. It was recently shown that the IDH-2 inhibitor AG-221 increased survival in a dose-dependent manner in a primary human IDH-2 mutant AML xenograft model. The initial step of CD45+ blast cell growth, which was followed by cellular differentiation, was linked to treatment with AG-221.[119] IDH-2 mutant leukemia is now the subject of a phase I investigation including AG-221 (NCT01915498). The combination of low-dose cytarabine and clofarabine resulted in a CR rate of sixty-three percent in a 2008 randomized study with seventy patients who were sixty years of age or older, as opposed to thirty-one percent when clofarabine was given alone. When administered intravenously for five days at doses of 20–30 mg/m^2, it has demonstrated effectiveness and safety as a single therapy for AML, with an approximate response rate of 40%.[120,121] A study of 320 relapsed/refractory AML patients over 55 found that clofarabine plus cytarabine increased CR, CR with inadequate platelet count, and DFS.[122] A study of 320 relapsed/refractory AML patients over 55 found that clofarabine plus cytarabine increased CR, CR with inadequate platelet count, and DFS.[123] Although there was no increase in OS in any of these investigations, these results suggest that clofarabine and cytarabine may work in concert. The results of a phase 2 trial including older patients taking low-dose cytarabine and newly diagnosed AML were recently revealed in a research study.[124] With a median age of 68 years, the 118 patients in this research were all 60 years of age or older. Days 2 through 10 of subcutaneous delivery of 20 mg/m^2 clofarabine and 20 mg low-dose cytarabine twice day were administered after the first day of induction therapy. The median OS and RFS had not been reached by the 10.9-month follow-up.[125] Patients with moderate-to-poor risk acute myeloid leukemia (AML) are being treated in a phase I/II study with frontline clofarabine, cytarabine, and idarubicin (NCT00838240).

Furthermore, studies are being conducted on the potential use of clofarabine in the post-transplant setting. Based on historical controls, the 2-year OS of 43% was good.[126] Although further RCTs are required to fully understand the role of clofarabine in AML, these investigations provide encouraging results for the drug, particularly when combined with cytarabine in elderly individuals. In addition to being administered intravenously, clofarabine has attracted interest as an oral drug for the treatment of AML. Unlike other purine nucleoside analogues, clofarabine can tolerate acidic pH levels and phosphorolytic cleavage by Escherichia coli in the stomach, which accounts for its 50% bioavailability.[127] A phase I/II trial included 35 people 60 years of age or older who had relapsed/refractory AML or high-risk MDS. The aim of the trial was to investigate the potential of oral clofarabine as a treatment for low-dose AML. A humanized recombinant antibody called Gemtuzumab ozogamicin (GO) targets the transmembrane protein CD33, which is expressed in cells of the myeloid lineage. Cells that express CD33 absorb the antibody once it binds to the deadly compound calicheamicin, which cleaves DNA. For the treatment of CD33-positive AML patients 60 years of age or older suffering their first relapse, the FDA authorized GO in 2000. The experiment was suddenly terminated after the FDA rescinded its approval. After the medicine was discontinued, recurrence rates reduced in a 2014 meta-analysis of five standardized clinical investigations.[128] Only those with a favourable or mild cytogenetic-risk profile had this survival impact, according to subgroup studies. In the most recent trial, 237 participants who were 60 years of age or older and unfit for intensive therapy were recruited. Patients who received appropriate supportive therapy together with GO induction and consolidation had a superior OS (hazard ratio of 0.69).[129] Again, this advantage was greatest for most survivors whose cytogenetic risk profile ranged between favorable and moderate. High concentrations of the transmembrane protein CD37 are present in developing B cells. It's likely that AGS67E's product, MMAE, can specifically target and kill cancer cells that express CD37. According to recent research, CD37 is expressed differently on the surface of AML stem cells that are CD34+ /CD38− compared to normal myeloid stem cells, where it is barely present. In a laboratory context, leukemic cells treated to nanomolar doses of AGS67E caused cytotoxicity, abnormal development, or death in seven out of sixteen investigated AML cell lines. Furthermore, in

a mouse xenograft model of AML, the treatment of AGS67E was demonstrated to drastically reduce tumor engraftment, leading to undetectable leukemic cell counts in three of the four AML samples. Thus, using CD37 as a prospective therapeutic target may enable the selective inhibition of leukemic cell proliferation. Chimeric antigen receptors, or CART intervention, are artificial T-cell receptors with an affinity similar to that of antibodies. They combine the intracellular and transmembrane domains of a T-cell receptor with the single-chain variable portion of a monoclonal antibody. Under such circumstances, one or more antigens may be precisely targeted by modifying a subset of host-derived chimeric antigen receptor-T (CART) cells. Despite the fact that benign and malignant CD19 cells cannot be distinguished from one another, patients experience remarkably low rates of morbidity after receiving this treatment. On the other hand, when normal myeloid lineage cells are reduced, persistent neutropenia makes it more difficult to treat AML using CART cell therapy. These CD33-specific CART cells have shown amazing effectiveness against AML cell lines in vitro.[130] In addition, AML xenograft survival was improved by CD33-specific CART therapy. Nonetheless, because CD33 is believed to combat tumors, it is present on healthy myeloid cells and has been connected to severe cytopenias. Through CD33-specific CAR mRNA electroporation of human T cells, researchers were able to produce anti-CD33 CAR. This may provide a therapeutically meaningful means of fighting tumors without ultimately impairing myelosuppression. Some have targeted the β folate receptor family member (FRβ) in order to target leukemic myeloid cells. Malignant myeloid hematopoietic cells express more of this receptor subtype.[131] Seventy percent of initial AML patients had FRβ expression, which may be further increased by all-trans retinoic acid therapy.[132,133] Recent studies have demonstrated the effects of FRβ-specific CART cell treatment in vitro and in an AML xenograft. CART cell therapy may provide relapsed or refractory acute myeloid leukaemia patients another treatment, even though it is still developing.

The chemotherapy medication cytarabine (Cytosar) is the foundation of the majority of induction therapies. Drugs used in targeted therapy or chemotherapy may be combined with this medication. The 7-and-3 protocol is usually used with cytarabine and anthracyclines, which are a group of chemotherapy drugs like daunorubicin, idarubicin, and mitoxantrone that damage DNA in cancer cells. After seven days of nonstop cytarabine administration, anthracycline is administered once a day for three days. Should certain genetic mutations exist, you will also be treated with targeted therapy. To help reduce white blood cell (WBC) counts, you might also be given hydroxyurea (Hydrea, Apo-hydroxyurea, and Mylan-hydroxyurea). Medications that could be utilized include: hypomethylating drugs like decitabine (Dacogen, Demylocan, and Inqovi) and azacitidine (Vidaza); low-concentration cytarabine; hypomethylating agents (azacitidine or decitabine); and venetoclax (Venclexta) or glasdegib (Daurismo) in low-dose combinations.

Targeted therapy

Targeted therapy stops the growth and spread of cancer by using medications to target specific molecules (like proteins) on cancer cells or inside them. One possible application for targeted therapy is induction treatment. If you have AML and a FLT3 gene mutation, you might be prescribed targeted therapy medications like midostaurin (Rydapt). In the event that your AML has a CD33 protein marker, you might be prescribed targeted therapy medications like gemtuzumab ozogamicin.

Central nervous system therapy

The brain and spinal cord make up the central nervous system (CNS). Intracerecal chemotherapy is one form of treatment that may be used if the leukemia has progressed to the central nervous system. Methotrexate, or cytarabine, is the medication used in intrathecal chemotherapy. It is typically administered during a spinal puncture. High-energy rays, or particles, are used in radiation therapy to kill cancer cells. It is occasionally administered to the spinal cord and brain in conjunction with intrathecal chemotherapy.

Supportive therapy

It is crucial to use supportive therapy at every stage of AML treatment. It is used to treat both the disease itself and the complications that frequently arise from AML treatments. During induction therapy, supportive therapies may be administered, such as: antivirals, antifungals, or antibiotics, to treat or prevent infections. Growth factors to aid in bone marrow recuperation following chemotherapy (chemotherapy can damage bone marrow, preventing it from producing enough healthy blood cells and raising infection risk). Transfusions of red blood cells, platelets, fresh frozen plasma, and cryoprecipitate -a substance that acts as a stand-in for clotting factors—are all available. Medications to lower elevated blood levels of certain chemicals that arise during the early stages of treatment when a large number of cancer cells die (known as tumour lysis syndrome). Leukapheresis to extract a significant amount of white blood cells from the circulation.

RELAPSED AML AND PROGNOSTIC FACTORS

Relapses in AML may be divided into three groups: molecular, extramedullary, and hematologic. Hematopoietic relapse is the term for when blast cells reappear and make up more than 5% of the bone marrow's cells; this is often viewed as a conclusive indicator. As will be discussed in the section on stem cell transplantation, it is important to measure the exact extent of leukemic bone marrow infiltration precisely because this information may influence the choice of treatment (Table 2). Extramedullary (EMD) recurrence can happen by itself or along with hematologic relapse, and it needs local radiation treatment and some kind of consolidation.[14,15] AML exhibiting granulocytic sarcoma and AML with t(8;21) are two examples of AMLs where it most commonly occurs. AML with core binding factor (CBF). Less commonly, the central nervous system (CNS) may be involved in the typical look of meningeal leukaemia. The frequency with which EMD recurs in patients with acute promyelocytic leukemia (APL) after all-trans retinoic acid (ATRA) treatment, either with or without chemotherapy, is an intriguing discovery. The brain, skin, and middle ear are the organs that are most often affected. However, the comprehensive study by Specchia et al. did clearly show that EMD recurrence is

rare in APL and that patients receiving ATRA along with chemotherapy (AIDA regimen) have a same chance of relapsing due to EMD as those receiving chemotherapy alone. Furthermore, the results of the inquiry demonstrated the patterns of the two cohorts. The study also showed that the two groups had different patterns of where the EMD was located, with patients who received ATRA having a higher frequency of CNS involvement when the disease came back.[19] Thus, prophylaxis with intrathecal chemotherapy should be considered for high-risk APL patients (defined as those with a white blood count greater than 10×10^6/L upon diagnosis). As of right now, therapy is only necessary for APL patients if a molecular relapse is identified.[21,22] It was clear from early GIMEMA group studies that individuals with APL who received treatment for molecular recurrence had a significantly better prognosis than those who received treatment for hematologic relapse. Not to mention, research has shown that monitoring the expression of the Wilms tumour 1 gene (WT1).

Table 2: Target and mechanism of action (MOA) of some of the selective and non-selective drugs used in the treatment of acute myeloid leukaemia (AML).

Selective	Target	MOA	Non-Selective	Target
Flavopiridol	CDK inhibitor	Cell-cycle arrest and apoptosis	Daunorubicin	Anthracycline
CD33-Targeted ADCs	CD33 target	Targeted delivery of toxic drug	Idarubicin	Anthracycline
Eltanexor	XPO1 inhibitor	XPO1 inhibition	Mitoxantrone	Anthracycline
Venetoclax	BCL-2 inhibitor	Anti-apoptotic Protein inhibition	Cytarabine (CPX351)	Pyrimidine analog
Sorafenib	FLT3 inhibitor	FLT3-ITD inhibition	Guadecitabine	Hypomethylation

PROGNOSTIC FACTORS FOR RELAPSED AML

When estimating the prognosis for individuals with newly diagnosed AML, many clinical and prognostic factors are significant. The CR rate and survival have been shown to be significantly influenced by age, cytogenetics, and preliminary blast clearance in particular. Research indicates that individuals who are young adults and have favorable cytogenetics tend to do better. Two classification schemes for chromosomal abnormalities have been developed by the South West Oncology Group in the United States and the Medical Research Council (MRC) Cooperative Group in the United Kingdom. These schemes have significant overlaps. So, when estimating the prognosis for individuals with newly diagnosed AML, many clinical and prognostic factors are significant. Better results have reportedly been recorded for young adolescents with good cytogenetics. The United States South West Oncology Group and the United Kingdom Medical Research Council (MRC) Cooperative group have created two largely overlapping categorization methods for chromosomal abnormalities.

Three groups can be identified

(i) a subset of patients with a better prognosis, comprising those with t(8;21), inv(16), and t(16;16), which account for 10-15% of cases and are more prevalent in individuals under 60.

(ii) a group with a poor outlook that includes people who have monosomies, long arm deletions of chromosomes 5 and 7, or problems with three or more chromosomes (complex karyotype). These people are usually older.

(iii) an intermediate group, which makes up 50–60% of cases with normal karyotypes and contains all other anomalies.

The South West Oncology Group in the United States and the Kingdom Medical Research Council (MRC) Cooperative Group 36 write that while the prognostic relevance of karyotype in primary AML is widely accepted, the value of cytogenetics at diagnosis for relapsed patients is not as well defined. Significantly, the patients' performance condition at relapse played a major role in their selection. The results of a retrospective multicenter research with 150 AML patients over 60 experiencing their first relapse revealed that 34% had undergone palliative care and 66% had received intensive treatment aimed at reaching CR2.44. Cytogenetics had a marginally significant impact on the subgroup of 100 patients undergoing intensive treatment ($p = 0.09$ in the multidimensional analysis). The CR1 length was the only parameter that was significantly correlated with the CR2 rate, DFS, and OS ($p = 0.09$ in the multidimensional analysis). Eight months was the median survival for patients whose CR1 lasted for more than twelve months, whereas the other group's median survival was just four months ($p = 0.002$). Similarly, $p = 0.001$ indicates that the median CR2 duration was eleven months as opposed to five months. Overall, after retrospectively analyzing a large cohort of 164 relapsed patients over 60 who were examined at our institution, we found that the median survival for patients undergoing intensive therapy and those handled with simple assistance was 5 and 3 months, respectively. Although statistically significant ($p = 0.03$), the therapeutic importance of this difference is quite minimal (Figure 2). Moreover, the effect of intense salvage chemotherapy vanished when treatment outcomes were limited to the subgroup of patients whose CR1 lasted less than 12 months (4 months vs. 3 months, $p = 0.10$). Post-CR1 therapy is the last thing that affects treatment outcomes. After CR1 is reinforced with chemotherapy and either autologous or allogeneic stem cell transplantation, it gradually worsens recurrent AML, CR2 rate, and duration.[7-10]

Stem cell therapy

Few studies highlight the possibility of stem cell transplantation in treating AML while taking into account access inequities and particular genetic variables. Autologous stem cell transplantation (ASCT) has been shown to be beneficial during a 125-month research period, with a 48% worldwide relapse-free survival at 5 years.[134] One possible way to treat acute myeloid leukaemia (AML) is to add medications or treatments that are specifically made to target leukaemia stem cells (LSCs) to the first-line treatment plan.[135] Retrospective studies have shown that reduced-intensity conditioning with Flu/Mel in combination with allogeneic stem cell transplantation is advantageous, particularly for young individuals with AML who are in their first complete

remission and have just received a diagnosis. According to a study conducted on 516 HSCT patients between 2010 and 2019, multiple myeloma was the most common cause for autologous HSCT and acute myeloid leukemia was the most common reason for allogeneic HSCT. Thirty-three percent of the patients had no illness at all, making the total 5-year survival rate of 65%.[136] All things considered, the research raises the prospect of using stem cell transplantation as an AML treatment, accounting for specific genetic traits and access disparities.

Initial study suggests that leukemic stem cells (LSCs) are restricted to the Lin−CD34+CD38− population, similar to HSCs that can restore normal hematopoiesis in NOD/SCID rats.[7] To improve xenograft transplant models, recent research has suppressed Natural Killer cell activity using anti-CD122 and used immune-deficient mouse strains like NOD/SCID/β2m−/− or NOD/SCID/IL2Rγ −/−. The original NOD/SCID model did not assist AML samples engraft, while subsequent models did. Additionally, LSC activity was seen in mature Lin−CD34+CD38+ progenitor populations in certain AML patients. The transplanted cell inoculum was injected intra-femorally instead of tail vein, improving disease transmission. LSC was found in multiple compartments and disease transmission efficiency was hierarchical. Limiting dilution investigations revealed a higher LSC frequency in Lin−CD34+CD38− individuals compared to Lin−CD34+CD38+ individuals. In all compartments, LSC were rare, with a frequency ranging from 1 in 1.6 $\times 10^3$ to 1 in 1.1×10^6 cells. These results show that AML's LSC compartment is more diversified and includes surface-committed progenitors. Note that normal Lin−CD34+CD38+ progenitor cells can only temporarily cure NOD/SCID mice and cannot repopulate secondary recipients. ALL research may increase LSC flexibility. Research indicates LSC potential in populations with progenitor characteristics (CD19+ and CD34−). CD34− populations not only transmitted leukemia to recipient mice, but also produced CD34+ progeny inside the transplanted leukemia. Recent mouse model data suggest AML LSC may be developmental plastic. Most CD34+ AML patients have both Lin−CD34+CD38−CD90−CD45RA+ and Lin−CD34+CD38+CD123+CD45RA+ LSC compartments, as shown by a complete comparison of the LSC phenotype with normal myeloid stem and progenit These populations resemble the usual lymphoid-primed multipotent progenitor (LMPP) and granulocyte-monocyte progenitor (GMP) populations phenotypically and molecularly. Most AML patients express CD34, while NPM1 mutation carriers have low CD34+ rates. LSC activity was confined to the CD34− population in individuals with less than 0.5% CD34+ cells, whereas in others, both groups had LSC. These studies demonstrate that the LSC population is phenotypically diverse and may vary considerably within and across patient subgroups. It is unclear how this represents the heterogeneity of the transformed target cell or cooperative mutations.

In addition to CD34 and CD38, LSC express CD33, CD123, and CD13. Recent research indicates that CD34+CD38− LSC express greater levels of novel markers than HSC. These include CLL-1, CD96, TIM3, CD47, CD32, and CD25. By diagnosis, 92% of AML patients' leukemic blasts had CLL-1. Normal HSC did not express this antigen, whereas CD34+CD38+ myeloid progenitors did. Like many LSC selective antigens, not all LSCs express it. In 29 AML patients, a median of 33% CLL-1+ cells were found in the CD34+CD38−LSC compartment. The Ig gene family contains CD96. More normal progenitors express it than HSC. CD34+CD38− LSC expression was higher in 65% of AML patients compared to normal HSC.Th-1-T cell immunity is inhibited by TIM3. The lower TIM3 expression of HSC compared to LSC facilitated LSC isolation in numerous AML patients. The ligand for signal-regulating protein α is the transmembrane protein CD47. Phagocytic cells express SIRPA and interact with CD47 to inhibit phagocytosis. Expression of CD47 by LSC protected them from macrophage and dendritic cell phagocytosis and decreased patient survival. LSC consistently expressed CD47 greater than HSC, although the proportion of LSC that did vary substantially across patients. Similarly, 34.4% and 24.6% of LSC from 61 AML patients contained the recently found LSC-specific markers CD25 and CD32.24 New LSC-specific markers have been discovered, however patient expression is still varied. Thus, patient-specific LSC surface antigen targeting may be essential (Fu)l (Table 3).[134-136]

Table 3: Hematopoietic stem cells and acute myeloid leukemia leukemic stem cells were analyzed to determine the expression of cell surface markers. + represents expression on marker on few or all cells. ++ represents the marker expressed at high level. – represents the marker is not present on specific stem cells.

Cluster of differentiation markers	Expression on stem cells (Leukemic)	Expression on stem cells (Hematopoietic)
CD123	++	+
CD34	+/-	+
CD38	+/-	-
CD45RA	+	-
CD90	-/+	+
CD44	++	+
CD96	++	+

Molecular targeted therapy

Among the well-known molecular treatments for AML are venetoclax, FLT3, and IDH1/2 inhibitors. Molecular abnormalities such FLT3, NPM1, KIT, and CEBPA mutations can be used to predict outcomes after allogeneic stem cell transplantation.[137] These mutations are also used to assess risk in addition to other biological traits. Gederitinib is authorized for relapsed/refractory FLT3-mutated AML, quizartinib for newly diagnosed AML with FLT3-ITD mutation, and midostaurin for newly diagnosed FLT3-mutated AML with conventional treatment, according an AML FLT3 inhibitor review. In spite of this, response rates following venetoclax remain low, emphasizing the necessity for innovative approaches to treating AML.[138] Based on multicenter, retrospective cohort studies

where venetoclax-based therapy was administered to individuals who had previously received treatment with FLT3, IDH1, or IDH2 inhibitors, venetoclax may be an effective salvage therapy for those individuals.[139] A study of the disease's molecular landscape that detailed almost 1,000 participants in Children's Oncology Group (COG) AML trials made it simpler to treat pediatric acute myeloid leukemia (AML) with age-tailored targeted treatments. Clinical trial participation is recommended while research is conducted to find novel molecular therapies and therapy combinations for AML.[140]

Notable progress has been made recently in the molecular targeted therapy of acute myeloid leukemia (AML), particularly with the identification of certain genetic abnormalities and aberrations that drive the disease. Many noteworthy characteristics and current clinical results are included. Principal goals and approaches with FLT3 inhibitors suggested authorized for use in patients with acute myeloid leukemia (AML) with a FLT3 mutation, midostaurin has been shown to improve overall survival when combined with chemotherapy (AC220 in the RATIFY trial). Gilteritinib, an oral FLT3 inhibitor with a response rate of around 50% in clinical trials, used in acute myeloid leukemia (AML) that has relapsed or is resistant to FLT3 mutations. Ivosidenib which targets specifically IDH1 mutations; shows promising results when used as monotherapy in patients with recently discovered IDH1 mutations as well as in situations where there has been a recurrence or resistance. Enasidenib has a response rate of around 40% and is specifically approved for treating IDH2 mutations in acute myeloid leukemia (AML) that has relapsed or is resistant to treatment. BCL-2 repressors like venetoclax given to elderly patients or those who are not suited for intensive chemotherapy in combination with hypomethylating medications (e.g., azacitidine). In clinical studies, the combination has shown an overall response rate of around 70%. EVI-1 (MECOM) Inhibitors experiment on the EVI1 gene are now being conducted to determine its relevance in acute myeloid leukemia (AML). Treatment aimed at CD33 with gemtuzumab ozogamicin, an antibody-drug combination that targets CD33; utilized in certain risk groups; has shown efficacy in older adults. Different targeted approaches and therapeutics under investigation that target mutations like TP53 and NPM1 are actively being investigated. The ADMIRAL research showed that in FLT3-mutated relapsed/refractory AML, gilteritinib improved overall survival relative to salvage chemotherapy, with a median overall survival of 9.3 months against 5.6 months for chemotherapy. Ivosidenib and azacitidine together produced an overall response rate of 73% in newly diagnosed patients with IDH1-mutated acute myeloid leukemia (AML), according to study published in Blood. In older patients with AML, the combination of venetoclax and Azacitidine has shown a median overall survival of 14.7 months, highlighting its significant benefit over traditional therapies. Final Evaluation on molecular customized therapeutics have transformed AML therapy, improving outcomes for those with certain genetic disorders. These approaches are being developed further via ongoing research and clinical trials, expanding the potential for customized AML therapy choices.[140]

Special situation management

Due to variations in disease biology, therapy tolerance, and long-term prognosis, AML in younger individuals may necessitate alternative methods to diagnosis and treatment than in older patients. Regardless of whether they adhere to an adult or pediatric strategy, treating adolescents and young adults (AYA) with AML can result in a 50% likelihood of cure.[141] This conclusion is based on the limited number of prospective and retrospective AYA studies. Based on a paired analysis of receiver operating characteristic (ROC) curves, research indicates that vitamin D medication may be helpful for individuals with AML.[142] Supportive care is crucial for treating treatment-associated problems in AML patients that are resistant or recurrent. Advanced therapies such as stem cell transplants, targeted medications (such as gemtuzumab ozogamicin), and clinical trial participation may be necessary.[143]

Myeloid sarcoma

Intensive induction chemotherapy regimens used in AML may be appropriate and practicable for treating patients with myeloid sarcoma, according to retrospective cohort research done at Memorial Hermann Hospital in Houston, Texas, focusing on six patients with biopsy-proven myeloid sarcoma.[143] According to different research, ELN-2017 risk classification has no effect on eAML/MS patient outcomes. Lowering early relapse rates in consolidation treatment seems to be accomplished with the use of HiDAC. The research also emphasizes the possible advantages of doing allo-BMT at the first CR.[144] The value of cytogenetic, molecular genetics, and immunohistochemical studies in supporting MS diagnosis is highlighted in another publication. It also highlights the fact that there are components of this condition that are uncertain, especially when it comes to the pediatric population.[145] According to a different review research, the majority of the literature suggests that isolated multiple sclerosis has a bad prognosis. When a child is diagnosed with AML, having extra medullary disease has not been shown to be a sign of a bad outlook. Instead, the outlook is likely based on more powerful factors, such as the molecular features of cancer cells.[146] In a study of 118 people with myeloid sarcoma, five who received low-dose decitabine maintenance treatment after transplant and 11 who received allo-HSCT lived without any recurrence.[147] This paper reports the discovery of myeloid sarcoma involving the thoracic spinal cord in a patient with acute spinal cord compression, who had progressed from myelofibrosis to AML. The patient had acute radiation treatment, but was unable to recover.[148]

Hyperleukocytosis

According to a different review of research, the majority of the literature suggests that isolated multiple sclerosis has a bad prognosis. When a child is diagnosed with AML, having extra medullary disease has not been shown to be a sign of a bad outlook. Instead, the outlook is likely based on more powerful factors, such as the molecular features of cancer cells.[149] In a study of 118 people with myeloid sarcoma, five who received low-dose decitabine maintenance treatment after transplant and 11 who received allo-HSCT lived without any recurrence.[147] This paper reports the discovery of myeloid sarcoma involving the thoracic spinal cord in a patient with acute spinal cord compression, who

had progressed from myelofibrosis to AML. The study shows that low-dose cytarabine is a safe cytoreduction strategy, and that hyperleukocytosis in 5–20% of newly diagnosed AML patients offers increased hazards. A 10-year retrospective case control study demonstrates that leukapheresis is safe and effective in treating pediatric acute leukaemia with hyperleukocytosis without postponing chemotherapy. It works even better because 13% of people who get leukapheresis end up dying from neurologic complications instead of the leukapheresis itself.[148] A case series with hyper leukocytic leukaemia found ALL instances with BCR/ABL fusion gene positivity and AML (M5 subtype). Leukapheresis may not lower induction mortality, according to different research that highlights the ongoing respiratory and central nervous system problems associated with hyperleukocytosis in spite of supportive treatment.[149,150]

Involvement of the CNS

Regardless of the need for a lumbar puncture, the CNS involvement in a retrospective analysis of 3240 newly diagnosed AML patients was modest (1.1%), and in another trial, intrathecal (IT) treatment showed quick success in reducing neurologic symptoms with little CSF recurrence.[151] Another study found that whereas higher recurrence rates are associated with CNS-AML, they do not independently predict survival after allo-HCT. Although patients with CNS involvement had shorter disease-free and overall survival durations than those without, the frequency of CNS involvement was equal in both groups of patients receiving high-dose cytarabine.[152] It is yet unknown how routine CNS prophylaxis affects DFS. Research indicates that allo-HSCT may be helpful since cytogenetic risk category, illness state, and chronic graft-versus-host disease are independent predictors of overall survival in CNS+AML. On the other hand, different research found that CNS involvement prior to allo-HSCT does not independently predict post-transplant survival.[153]

Pregnancy

Leukemia-affected pregnant women are more likely to have intrauterine growth restriction, abortion, and perinatal mortality.[154,155] A retrospective study that took place between January 2010 and January 2021 involved 25 pregnant women with newly diagnosed AML.[156,157] Twelve of them underwent therapeutic abortions, and 13 gave birth to their children—four at full term and nine preterm.[158,159] An additional evaluation spanning from 2010 to 2019 recommended starting chemotherapy early to boost full response rates. It also highlighted the need for voluntary termination or induced birth prior to treatment to improve outcomes for both the mother and the foetus.[160,161] AML chemotherapy outcomes are unaffected by pregnancy, according

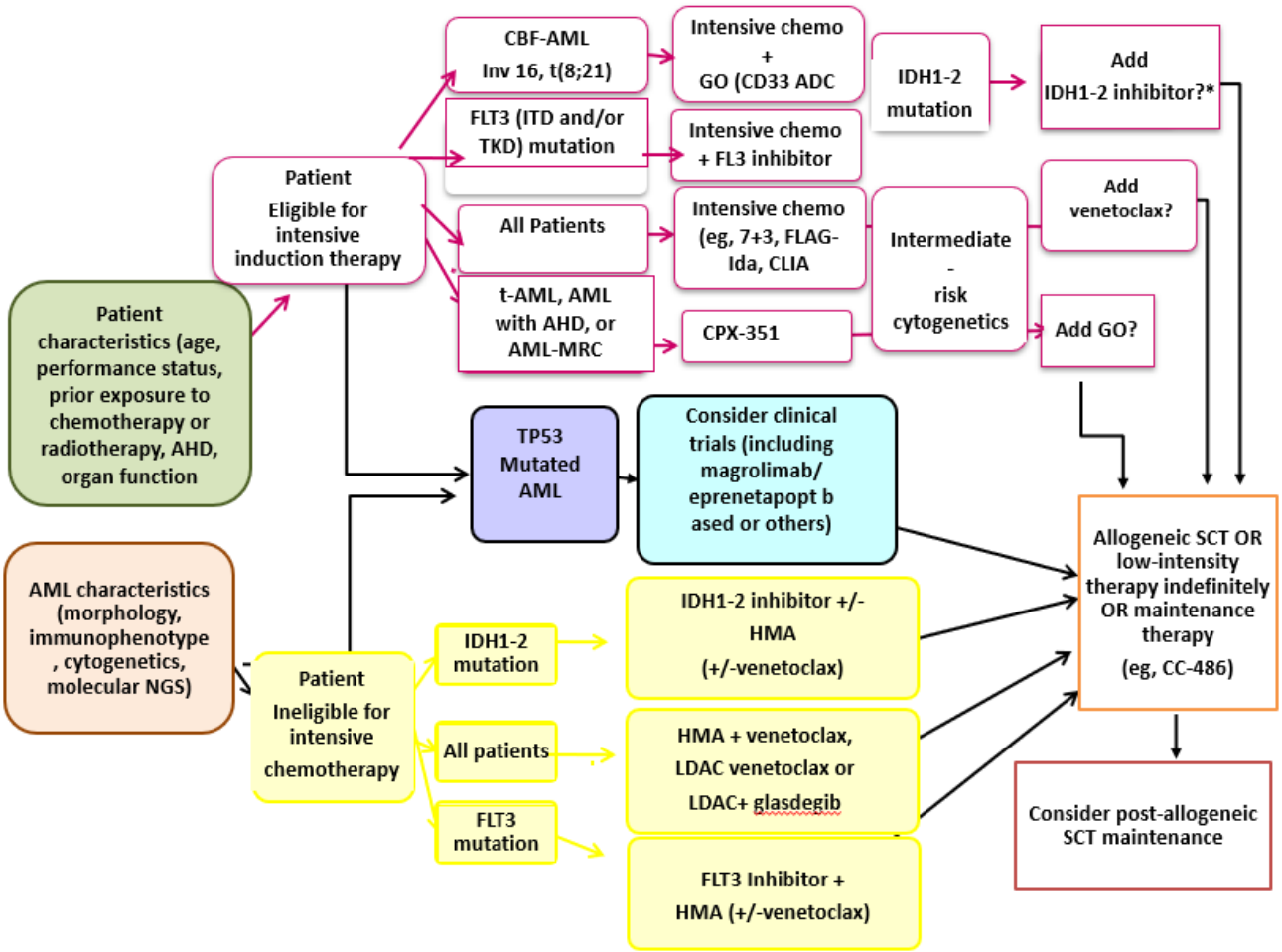

Figure 4. Advances in the diagnostic and treatment paradigm for recently diagnosed AML.

to study results, which warn against treatment delays that might worsen maternal outcomes without improving pregnancy outcomes.[162-166] Research on AML and chronic myeloid leukaemia during pregnancy suggests that normal births may be possible with imatinib and chemotherapy, respectively (Figure 4).

RECENT UPDATES ON META-ANALYSIS AND SYSTEMATIC APPROACHES WITH RANDOM CONTROL TRIALS (RCT)

One emerging method that allows for the simultaneous evaluation of several therapeutic options - some of which may not have received as much attention in the original research investigations - is meta-analysis. Most meta-analyses of networks have only included RCT data. Rarely, one may consider non-randomized studies. RCT limitations may be strengthened or circumvented by non-randomized research. These limitations include limited sample sizes, brief follow-ups, restricted participant selection, and ethical considerations. Because of its many forms and inconsistent reactions to therapy, AML poses a number of difficulties. In order to identify novel patterns in AML therapy, meta-analysis synthesizes data from several research, including cohort and clinical trials, to illuminate these trends and predictions.[167-172] For each induction type, the following parameters were assessed: myelotoxicity (median duration until neutrophil recovery [>1.0 × 10^9/L], platelet recovery [>100 × 10^9/L], hospitalization duration), AML outcomes (median disease-free, overall survival, CR, induction deaths), and prognostic (age, performance status, unfavorable cytogenetics, antecedent malignancy) (Table 4). Using both direct and indirect evidence, we computed the odds ratio (OR) for each therapy in relation to the reference induction treatment, which was the most widely used combination of standard-dose cytarabine (100 mg/m^2 for 7–10 days) and daunorubicin (30–60 mg/m^2 for 3 days). The results of the meta-analysis indicated a significant correlation ($p < 0.05$) between a longer time from diagnosis to therapy and a lower chance of achieving full remission.[173-178]

Table 4: Summary of the goals and findings of several study kinds pertaining to AML and its treatment (meta-analysis).

Objective	Key outcomes	Ref.
Consensus regarding the prognostic impact of time from diagnosis to treatment (TDT) in AML.	The extremely diverse results indicate that, in clinically stable individuals, especially those 60 years of age and beyond, it would be possible to undertake cytogenetic/molecular testing.	169
To find evidence-based medical studies and no definitive treatment guidelines	According to the findings, there may be a connection between hepatitis C virus infection and environmental exposure, including interior design, and AML risk.	170
To understand the trends and determinants by combining data from many research, including clinical trials and cohort studies, to identify emerging patterns in AML therapy.	This meta-analysis highlights the significance of continuous research and individualized therapy approaches, providing insightful information about AML treatment.	171
to evaluate the effectiveness and safety of treating AML with venetoclax (VEN) in addition to chemotherapy (chemo) vs chemo alone.	In individuals with AML, the VEN+chemotherapy shows a notable safety profile and effectiveness.	172
In individuals with untreated acute myeloid leukemia who are not eligible for intensive chemotherapy, this network meta-analysis (NMA) evaluated the effectiveness of venetoclax (VEN) + azacitidine (AZA) and VEN + low-dose cytarabine (LDAC) in comparison with AZA, LDAC, and decitabine monotherapies and best supportive care (BSC).	Patients with treatment-naive acute myeloid leukemia who were not eligible for intense chemotherapy showed better effectiveness with VEN + AZA and VEN + LDAC when compared to other regimens.	173
To examine the main and secondary outcomes used in phase III randomized controlled trials (RCTs) for AML.	Throughout the last 15 years, there has been an increase in the adoption of the clinically significant and objective goal of overall survival.	174
To calculate the relative efficacy of induction therapies for older AML patients.	While most of the studied regimens seemed to have comparable effectiveness profiles, certain induction regimens showed considerable changes when compared to the reference induction. However, as indirect comparisons dominated the network, these findings should be taken cautiously.	175
To comprehensively examine the evidence supporting maintenance therapy in AML patients after completion of consolidation chemotherapy or HCT.	Survivorship has always been the most sought-after result in AML studies. Survival is not the sole significant result in RCTs, however, and future studies should prioritize quality of life (QoL) as their endpoint.	176
Preventing illness recurrences is a critical problem in AML therapy. Although intense consolidation treatment works, maintenance therapy is disputed.	The present study successfully replaced the conventional postremission therapy of the Japan Adult Leukemia Study Group, which consisted of three courses of standard-dose consolidation and six courses of maintenance therapy. The shorter duration of four courses of standard-dose consolidation therapy was used instead of additional maintenance therapy.	177

DISCUSSION

Through the development of novel therapeutic approaches and a better understanding of the disease's molecular underpinnings, the area of AML research and treatment has made significant strides. Current perspectives highlight the need of personalized therapy, in which care plans are tailored to the individual genetic

and molecular traits of each patient's leukemia. Because cytogenetic abnormalities and different genetic mutations have a substantial impact on prognosis and therapeutic response, this approach recognizes the heterogeneity of AML. Cytotoxic chemotherapy, primarily using medications like cytarabine and anthracyclines (e.g., daunorubicin), has been the standard treatment for AML for a long time. New developments have provided immunotherapeutic options and tailored medications.

While venetoclax, when used with hypomethylating medications, has shown effectiveness, particularly in elderly patients or those who are not appropriate for intensive chemotherapy, medications like midostaurin and gilteritinib explicitly target mutations in the FLT3 gene. Additional customized treatment options that lessen systemic toxicity are made possible by the development of antibody-drug conjugates, such as gemtuzumab ozogamicin. Checkpoint inhibitors, which strengthen the immune response against leukemic cells, and tiny drugs that precisely target pathways associated in leukaemia formation, such as IDH1/2 and BCL-2 inhibitors, are examples of novel therapeutics for acute myeloid leukemia (AML). Additionally, while challenges remain in achieving sustained remissions, the potential of CAR T-cell therapy and bispecific T-cell engagers represents a significant advancement in immunotherapy for AML. More attention is needed in several areas of AML research. Since interactions with stromal cells may influence the development of illness and treatment resistance, studying the microenvironment of leukaemic cells is an essential component. Acknowledging the role of epigenetics in AML, namely the effects of histone modifications and DNA methylation, may also provide new therapeutic targets and predictors of treatment response. Examining methods for detecting minimal residual disease (MRD) is another intriguing strategy. Improved methods for identifying MRD might guide treatment decisions and suggest further therapies following remission. To improve treatment plans and outcomes for a variety of patient groups, it is also essential to look at patient-specific factors including age, comorbidities, and genetic predispositions.[175-178]

Conclusion and Future Prospects

Characteristically and physiologically, AML is a heterogeneous condition. Long-term survival rates are still quite low, despite advances in supportive care and predictive risk assessment leading to improvements in standard therapy. Most cases that are newly diagnosed occur in older people, who are more likely to have a poor cytogenetic profile. But these patients often cannot get the best care or stem cell transplantation because of their increased risk of TRM. Innovative treatments may reduce off-target toxicity and improve leukaemia treatment. Given the genetic variability of AML, it appears unlikely that a single "magic bullet" treatment would emerge from targeted medications such as FLT3 tyrosine kinase inhibitors. Rather, when innovative medications are introduced in conjunction with improved genetic screening and risk categorization, incremental increases in survival and remission may be expected. Also, special markers on the surface of cells could be used as a therapeutic target for chimeric antigen receptors or recombinant monoclonal antibodies. Enzymes that have been changed and pathways that have been turned on could also be used. The challenge in this case is to selectively target leukemic myeloid cells while maintaining non-malignant myeloid progenitors. Last but not least, the treatment choices available to elderly patients—who are more likely to die from traditional chemotherapy regimens—would be increased with the advent of well-tolerated oral medicines like clofarabine. With cutting-edge medications at the forefront of AML therapy, we want to bring in a new age of enhanced reactions.

Author Contributions

The study was conceptualized, designed, and an original draft prepared by KA and KG; NR, PB and SM developed the method and data extraction; RM reviewed and revised the overall manuscript. The final manuscript was read and approved by all the authors.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

Authors thanks the Director of Paramedical College, Durgapur, and Principal, Bankura Christian College, for their constant support for this work.

References

1. J.F. Yamamoto, M.T. Goodman. Patterns of leukemia incidence in the United States by subtype and demographic characteristics, 1997-2002. *Cancer Causes Control* **2008**, 19 (4), 379–390.
2. B.S. Chhikara, K. Parang. Global Cancer Statistics 2022: the trends projection analysis. *Chem. Biol. Lett.* **2023**, 10 (1), 451.
3. A. Shah, T.M.L. Andersson, B. Rachet, M. Björkholm, P.C. Lambert. Survival and cure of acute myeloid leukaemia in England, 1971-2006: a population-based study. *Br. J. Haematol.* **2013**, 162 (4), 509–516.
4. J. Meyers, Y. Yu, J.A. Kaye, K.L. Davis. Medicare fee-for-service enrollees with primary acute myeloid leukemia: An analysis of treatment patterns, survival, and healthcare resource utilization and costs. *Appl. Health Econ. Health Policy* **2013**, 11 (3), 275–286.
5. H. Sill, W. Olipitz, A. Zebisch, E. Schulz, A. Wölfler. Therapy-related myeloid neoplasms: Pathobiology and clinical characteristics. *Br. J. Pharmacol.* **2011**, 162 (4), 792–805.
6. P. Van Vlierberghe, A. Ambesi-Impiombato, I. Rigo, et al. Prognostic Relevance of Integrated Genetic Profiling in Adult T-Cell Acute Lymphoblastic Leukemia. *Blood* **2012**, 120 (21), 294–294.
7. P. Voigt, D. Reinberg. Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia The Cancer Genome Atlas Research Network. *N. Engl. J. Med.* **2013**, 368 (22), 2059–2074.
8. D. Gary Gilliland, J.D. Griffin. The roles of FLT3 in hematopoiesis and leukemia. *Blood* **2002**, 100 (5), 1532–1542.
9. S. Takahashi. Current findings for recurring mutations in acute myeloid leukemia. *J. Hematol. Oncol.* **2011**, 4, 36.
10. R. Kihara, Y. Nagata, H. Kiyoi, et al. Comprehensive analysis of genetic alterations and their prognostic impacts in adult acute myeloid leukemia patients. *Leukemia* **2014**, 28 (8), 1586–1595.
11. A.M. Cook, L. Li, Y. Ho, et al. Role of altered growth factor receptor-mediated JAK2 signaling in growth and maintenance of human acute myeloid leukemia stem cells. *Blood* **2014**, 123 (18), 2826–2837.
12. S. Ghoshal (Gupta), H. Baumann, M. Wetzler. Epigenetic regulation of signal transducer and activator of transcription 3 in acute myeloid leukemia. *Leuk. Res.* **2008**, 32 (7), 1005–1014.

13. O. Yamada, K. Kawauchi. The role of the JAK-STAT pathway and related signal cascades in telomerase activation during the development of hematologic malignancies. *Jak-Stat* **2013**, 2 (4), e25256.
14. J.J. Schuringa, A.T.J. Wierenga, W. Kruijer, E. Vellenga. Constitutive Stat3, Tyr705, and Ser727 phosphorylation in acute myeloid leukemia cells caused by the autocrine secretion of interleukin-6. *Blood* **2000**, 95 (12), 3765–3770.
15. K. Spiekermann, K. Bagrintseva, R. Schwab, K. Schmieja, W. Hiddemann. Overexpression and constitutive activation of FLT3 induces STAT5 activation in primary acute myeloid leukemia blast cells. *Clin. Cancer Res.* **2003**, 9 (6), 2140–2150.
16. D.P. Steensma, R.F. McClure, J.E. Karp, et al. JAK2 V617F is a rare finding in de novo acute myeloid leukemia, but STAT3 activation is common and remains unexplained. *Leukemia* **2006**, 20 (6), 971–978.
17. U. Creutzig, M.M. Van Den Heuvel-Eibrink, B. Gibson, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: Recommendations from an international expert panel. *Blood* **2012**, 120 (16), 3167–3205.
18. J.W. Vardiman, J. Thiele, D.A. Arber, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: Rationale and important changes. *Blood* **2009**, 114 (5), 937–951.
19. E.Y. Skolnik, A. Batzer, N. Li, et al. The Function of GRB2 in Linking the Insulin Receptor to Ras Signaling Pathways. *Science (80-.).* **1993**, 260 (5116), 1953–1955.
20. N. Li, A. Batzer, R. Daly, et al. Guanine-nucleotide-releasing factor hSos1 binds to Grb2 and links receptor tyrosine kinases to Ras signalling. *Nature* **1993**, 363 (6424), 85–88.
21. E.J. Lowenstein, R.J. Daly, A.G. Batzer, et al. The SH2 and SH3 domain-containing protein GRB2 links receptor tyrosine kinases to ras signaling. *Cell* **1992**, 70 (3), 431–442.
22. M. Rozakis-Adcock, J. McGlade, G. Mbamalu, et al. Association of the Shc and Grb2/Sem5 SH2-containing proteins is implicated in activation of the Ras pathway by tyrosine kinases. *Nature* **1992**, 360 (6405), 689–692.
23. S.M. Thomas, M. DeMarco, G. D'Arcangelo, S. Halegoua, J.S. Brugge. Ras is essential for nerve growth factor- and phorbol ester-induced tyrosine phosphorylation of MAP kinases. *Cell* **1992**, 68 (6), 1031–1040.
24. X.F. Zhang, J. Settleman, J. Kyriakis, et al. Normal and oncogenic p21ras proteins bind to the amino-terminal regulatory domain of c-Raf-1. *Nature* **1993**, 364 (6435), 308–313.
25. T.G. Boulton, S.H. Nye, D.J. Robbins, et al. ERKs: A family of protein-serine/threonine kinases that are activated and tyrosine phosphorylated in response to insulin and NGF. *Cell* **1991**, 65 (4), 663–675.
26. T.G. Boulton, G.D. Yancopoulos, J.S. Gregory, et al. An Insulin-Stimulated Protein Kinase Similar to Yeast Kinases Involved in Cell Cycle Control. *Science (80-.).* **1990**, 249 (4964), 64–67.
27. D.J. Robbins, M. Cheng, E. Zhen, et al. Evidence for a Ras-dependent extracellular signal regulated protein kinase (ERK) cascade. *Proc. Natl. Acad. Sci* 89, 6924–6928.
28. K.W. Wood, C. Sarnecki, T.M. Roberts, J. Blenis. ras mediates nerve growth factor receptor modulation of three signal-transducing protein kinases: MAP kinase, Raf-1, and RSK. *Cell* **1992**, 68 (6), 1041–1050.
29. S.H. Yang, A.D. Sharrocks, A.J. Whitmarsh. Transcriptional regulation by the MAP kinase signaling cascades. *Gene* **2003**, 320 (1–2), 3–21.
30. H. Gu, K. Saito, L.D. Klaman, et al. Essential role for Gab2 in the allergic response. *Nature* **2001**, 412 (6843), 186–190.
31. H. Serve, N.S. Yee, G. Stella, et al. Differential roles of PI3-kinase and Kit tyrosine 821 in Kit receptor-mediated proliferation, survival and cell adhesion in mast cells. *EMBO J.* **1995**, 14 (3), 473–483.
32. R. Loewith. TOR Signalling. *Encycl. Mol. Pharmacol.* **2008**, 1212–1217.
33. T.F. Franke, C.P. Hornik, L. Segev, G.A. Shostak, C. Sugimoto. PI3K/Akt and apoptosis: size matters. *Oncogene* 22, 8983–8998.
34. P. Rodriguez-Viciana, P.H. Warne, R. Dhand, et al. Phosphatidylinositol-3-OH kinase direct target of Ras. *Nature* **1994**, 370 (6490), 527–532.
35. X. Cao, A. Tay, G.R. Guy, Y.H. Tan. Activation and Association of Stat3 with Src in v-Src-Transformed Cell Lines. *Mol. Cell. Biol.* **1996**, 16 (4), 1595–1603.
36. C.L. Yu, D.J. Meyer, G.S. Campbell, et al. Enhanced DNA-binding activity of a stat3-related protein in cells transformed by the Src oncoprotein. *Science (80-.).* **1995**, 269 (5220), 81–83.
37. Z. Wen, Z. Zhong, J.E. Darnell. Maximal activation of transcription by statl and stat3 requires both tyrosine and serine phosphorylation. *Cell* **1995**, 82 (2), 241–250.
38. X. Zhang, J. Blenis, H.C. Li, C. Schindler, S. Chen-Kiang. Requirement of serine phosphorylation for formation of STAT-promoter complexes. *Science (80-.).* **1995**, 267 (5206), 1990–1994.
39. T. Nosaka, T. Kawashima, K. Misawa, et al. STAT5 as a molecular regulator of proliferation, differentiation and apoptosis in hematopoietic cells. *EMBO J.* **1999**, 18 (17), 4754–4765.
40. G. Behre, S.M. Singh, H. Liu, et al. Ras signaling enhances the activity of C/EBPα to induce granulocytic differentiation by phosphorylation of serine 248. *J. Biol. Chem.* **2002**, 277 (29), 26293–26299.
41. I. Matsumura, A. Kawasaki, H. Tanaka, et al. Biologic significance of GATA-1 activities in RAS-mediated megakaryocytic differentiation of hematopoietic cell lines. *Blood* **2000**, 96 (7), 2440–2450.
42. M. Gabbianelli, E. Pelosi, E. Montesoro, et al. Multi-level effects of flt3 ligand on human hematopoiesis: Expansion of putative stem cells and proliferation of granulomonocytic progenitors/monocytic precursors. *Blood* **1995**, 86 (5), 1661–1670.
43. L.S. Rusten, S.D. Lyman, O.P. Veiby, S.E.W. Jacobsen. The FLT3 ligand is a direct and potent stimulator of the growth of primitive and committed human CD34+ bone marrow progenitor cells in vitro. *Blood* **1996**, 87 (4), 1317–1325.
44. M. Mizuki, J. Schwäble, C. Steur, et al. Suppression of myeloid transcription factors and induction of STAT response genes by AML-specific Flt3 mutations. *Blood* **2003**, 101 (8), 3164–3173.
45. R. Zheng, A.D. Friedman, M. Levis, et al. Internal tandem duplication mutation of FLT3 blocks myeloid differentiation through suppression of C/EBPα expression. *Blood* **2004**, 103 (5), 1883–1890.
46. R. Zheng, A.D. Friedman, D. Small. Targeted inhibition of FLT3 overcomes the block to myeloid differentiation in 32Dcl3 cells caused by expression of FLT3/ITD mutations. *Blood* **2002**, 100 (12), 4154–4161.
47. D.A. Arber, A. Orazi, R. Hasserjian, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* **2016**, 127 (20), 2391–2405.
48. H. Kantarjian, S. O'Brisn, J. Cortes, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: Predictive prognostic models for outcome. *Cancer* **2006**, 106 (5), 1090–1098.
49. R.B. Walter, M. Othus, G. Borthakur, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: A novel paradigm for treatment assignment. *J. Clin. Oncol.* **2011**, 29 (33), 4417–4423.
50. E. Hulegårdh, C. Nilsson, V. Lazarevic, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: A report from the Swedish Acute Leukemia Registry. *Am. J. Hematol.* **2015**, 90 (3), 208–214.
51. E.H. Estey. Acute myeloid leukemia: 2014 Update on risk-stratification and management. *Am. J. Hematol.* **2014**, 89 (11), 1063–1081.
52. K. Mrózek, G. Marcucci, D. Nicolet, et al. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. *J. Clin. Oncol.* **2012**, 30 (36), 4515–4523.
53. Y.Z. Qin, H.H. Zhu, Q. Jiang, et al. Prevalence and prognostic significance of c-KIT mutations in core binding factor acute myeloid leukemia: A comprehensive large-scale study from a single Chinese center. *Leuk. Res.* **2014**, 38 (12), 1435–1440.

54. P. Paschka, G. Marcucci, A.S. Ruppert, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): A Cancer and Leukemia Group B study. *J. Clin. Oncol.* **2006**, 24 (24), 3904–3911.
55. S.H. Park, H.S. Chi, S.K. Min, et al. Prognostic impact of c-KIT mutations in core binding factor acute myeloid leukemia. *Leuk. Res.* **2011**, 35 (10), 1376–1383.
56. S.H. Park, H.J. Lee, I.S. Kim, et al. Incidences and prognostic impact of c-KIT, WT1, CEBPA, and CBL mutations, and mutations associated with epigenetic modification in core binding factor acute myeloid leukemia: A multicenter study in a Korean population. *Ann. Lab. Med.* **2015**, 35 (3), 288–297.
57. K. Döhner, R.F. Schlenk, M. Habdank, et al. Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: Interaction with other gene mutations. *Blood* **2005**, 106 (12), 3740–3746.
58. H.Y. Li, D.H. Deng, Y. Huang, et al. Favorable prognosis of biallelic CEBPA gene mutations in acute myeloid leukemia patients: A meta-analysis. *Eur. J. Haematol.* **2015**, 94 (5), 439–448.
59. S. Fröhling, R.F. Schlenk, J. Breitruck, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: A study of the AML study group Ulm. *Blood* **2002**, 100 (13), 4372–4380.
60. M. Port, M. Böttcher, F. Thol, et al. Prognostic significance of FLT3 internal tandem duplication, nucleophosmin 1, and CEBPA gene mutations for acute myeloid leukemia patients with normal karyotype and younger than 60 years: A systematic review and meta-analysis. *Ann. Hematol.* **2014**, 93 (8), 1279–1286.
61. A. Cagnetta, S. Adamia, C. Acharya, et al. Role of genotype-based approach in the clinical management of adult acute myeloid leukemia with normal cytogenetics. *Leuk. Res.* **2014**, 38 (6), 649–659.
62. R.E. Gale, C. Green, C. Allen, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood* **2008**, 111 (5), 2776–2784.
63. S. Schnittger, U. Bacher, C. Haferlach, et al. Diversity of the juxtamembrane and TKD1 mutations (Exons 13-15) in the FLT3 gene with regards to mutant load, sequence, length, localization, and correlation with biological data. *Genes Chromosom. Cancer* **2012**, 51 (10), 910–924.
64. V. Grossmann, S. Schnittger, A. Kohlmann, et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. *Blood* **2012**, 120 (15), 2963–2972.
65. V. Shivarov, R. Gueorguieva, A. Stoimenov, R. Tiu. DNMT3A mutation is a poor prognosis biomarker in AML: Results of a meta-analysis of 4500 AML patients. *Leuk. Res.* **2013**, 37 (11), 1445–1450.
66. C.D. Dinardo, F. Ravandi, S. Agresta, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. *Am. J. Hematol.* **2015**, 90 (8), 732–736.
67. X. Chen, H. Xie, B.L. Wood, et al. Relation of clinical response and minimal residual disease and their prognostic impact on outcome in acute myeloid leukemia. *J. Clin. Oncol.* **2015**, 33 (11), 1258–1264.
68. R.B. Walter, H.M. Kantarjian, X. Huang, et al. Effect of complete remission and responses less than complete remission on survival in acute myeloid leukemia: A combined Eastern Cooperative Oncology Group, Southwest Oncology Group, and M. D. Anderson Cancer Center study. *J. Clin. Oncol.* **2010**, 28 (10), 1766–1771.
69. M. Hoyos, J.F. Nomdedeu, J. Esteve, et al. Core binding factor acute myeloid leukemia: The impact of age, leukocyte count, molecular findings and minimal residual disease. *Eur. J. Haematol.* **2013**, 91 (3), 209–218.
70. J.A. Liu Yin, M.A. O'Brien, R.K. Hills, et al. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: Results of the United Kingdom MRC AML-15 trial. *Blood* **2012**, 120 (14), 2826–2835.
71. M.J.L. Aitken, F. Ravandi, K.P. Patel, N.J. Short. Prognostic and therapeutic implications of measurable residual disease in acute myeloid leukemia. *J. Hematol. Oncol.* **2021**, 14 (1), 332–341.
72. D.J. Carey, S.N. Fetterolf, F.D. Davis, et al. The Geisinger MyCode community health initiative: An electronic health record-linked biobank for precision medicine research. *Genet. Med.* **2016**, 18 (9), 906–913.
73. A. Hubel, R. Spindler, A.P.N. Skubitz. Storage of human biospecimens: Selection of the optimal storage temperature. *Biopreserv. Biobank.* **2014**, 12 (3), 165–175.
74. S. Buchrits, A. Gafter-Gvili, J. Bishara, et al. The importance of abnormal platelet count in patients with clostridioides difficile infection. *J. Clin. Med.* **2021**, 10 (13), 2957.
75. B. Morrell, W. Lipworth, R. Axler, I. Kerridge, M. Little. Cancer as rubbish: Donation of tumor tissue for research. *Qual. Health Res.* **2011**, 21 (1), 75–84.
76. R.J. Bonnie, E.P. Backes. National Academies of Sciences, Engineering, and Medicine. The Promise of Adolescence: Realizing Opportunity for All Youth. *Div. Behav. Soc. Sci. Educ.* **2019**.
77. A. Ferrari, D. Stark, F.A. Peccatori, et al. Adolescents and young adults (AYA) with cancer: a position paper from the AYA Working Group of the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOPE). *ESMO Open* **2021**, 6 (2), 100096.
78. S. Buchrits, A. Gafter-Gvili, J. Bishara, et al. The importance of abnormal platelet count in patients with clostridioides difficile infection. *J. Clin. Med.* **2021**, 10 (13), 2957.
79. S.A. Buckley, F.R. Appelbaum, R.B. Walter. Prognostic and therapeutic implications of minimal residual disease at the time of transplantation in acute leukemia. *Bone Marrow Transplant.* **2013**, 48 (5), 630–641.
80. M.B. Vidriales, E. Pérez-López, C. Pegenaute, et al. Minimal residual disease evaluation by flow cytometry is a complementary tool to cytogenetics for treatment decisions in acute myeloid leukaemia. *Leuk. Res.* **2015**, 40, 1–9.
81. Q. Gong, L. Zhou, S. Xu, et al. High doses of daunorubicin during induction therapy of newly diagnosed acute myeloid leukemia: A systematic review and meta-analysis of prospective clinical trials. *PLoS One* **2015**, 10 (5), 125612.
82. X. Li, S. Xu, Y. Tan, J.P. Chen. The effects of idarubicin versus other anthracyclines for induction therapy of patients with newly diagnosed leukaemia. *Cochrane Database Syst. Rev.* **2015**, 2015 (6), 10432.
83. B. Löwenberg. Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. *Blood* **2013**, 121 (1), 26–28.
84. B. Lowenberg, T. Pabst, E. Vellenga, et al. Cytarabine Dose for Acute Myeloid Leukemia. *N. Engl. J. Med.* **2011**, 364 (22), 2166–2169.
85. H. Dombret, J.F. Seymour, A. Butrym, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* **2015**, 126 (3), 291–299.
86. E. Padron, H. Fernandez. Anthracycline dose intensification in young adults with acute myeloid leukemia. *Ther. Adv. Hematol.* **2012**, 3 (1), 17–27.
87. A.M. Carella, N. Cascavilla, M.M. Greco, et al. Treatment of "poor risk" acute myeloid leukemia with Fludarabine, Cytarabine and G-CSF (Flag regimen): A single center study. *Leuk. Lymphoma* **2001**, 40 (3–4), 295–303.
88. R.H. Herzig, H.M. Lazarus, S.N. Wolff, G.L. Phillips. High-dose cytosine arabinoside therapy with and without anthracycline antibiotics for remission reinduction of acute nonlymphoblastic leukemia. *J. Clin. Oncol.* **1985**, 3 (7), 992–997.
89. S. Amadori, W. Arcese, G. Isacchi, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: An effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. *J. Clin. Oncol.* **1991**, 9 (7), 1210–1214.
90. S. Daenen, B. Löwenberg, P. Sonneveld, et al. Efficacy of etoposide and mitoxantrone in patients with acute myelogenous leukemia

refractory to standard induction therapy and intermediate-dose cytarabine with amsidine. *Leukemia* **1994**, 8 (1), 6–10.
91. T. Büchner, R.F. Schlenk, M. Schaich, et al. Acute Myeloid Leukemia (AML): Different treatment strategies versus a common standard arm - Combined prospective analysis by the German AML Intergroup. *J. Clin. Oncol.* **2012**, 30 (29), 3604–3610.
92. J. Koreth, R. Schlenk, K.J. Kopecky, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: Systematic review and meta-analysis of prospective clinical trials. *Jama* **2009**, 301 (22), 2349–2361.
93. M. Yanada, K. Matsuo, N. Emi, T. Naoe. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: A metaanalysis. *Cancer* **2005**, 103 (8), 1652–1658.
94. J.K. Weick, K.J. Kopecky, F.R. Appelbaum, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: A Southwest Oncology Group study. *Blood* **1996**, 88 (8), 2841–2851.
95. M. Stelljes, U. Krug, D.W. Beelen, et al. Allogeneic transplantation versus chemotherapy as postremission therapy for acute myeloid leukemia: A prospective matched pairs analysis. *J. Clin. Oncol.* **2014**, 32 (4), 288–296.
96. R.F. Schlenk, K. Döhner, J. Krauter, et al. Mutations and Treatment Outcome in Cytogenetically Normal Acute Myeloid Leukemia. *N. Engl. J. Med.* **2008**, 358 (18), 1909–1918.
97. C. Röllig, M. Bornhäuser, M. Kramer, et al. Allogeneic stem-cell transplantation in patients with NPM1-mutated acute myeloid leukemia: Results from a prospective donor versus no-donor analysis of patients after upfront HLA typing within the SAL-AML 2003 trial. *J. Clin. Oncol.* **2015**, 33 (5), 403–410.
98. J.J. Cornelissen, W.L.J. Van Putten, L.F. Verdonck, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: Benefits for whom? *Blood* **2007**, 109 (9), 3658–3666.
99. J. Schetelig, M. Schaich, K. Schäfer-Eckart, et al. Hematopoietic cell transplantation in patients with intermediate and high-risk AML: results from the randomized Study Alliance Leukemia (SAL) AML 2003 trial. *Leukemia* **2015**, 29 (5), 1060–1068.
100. D. Li, L. Wang, H. Zhu, et al. Efficacy of allogeneic hematopoietic stem cell transplantation in intermediate-risk acute myeloid leukemia adult patients in first complete remission: A meta-analysis of prospective studies. *PLoS One* **2015**, 10 (7), 132620.
101. R.F. Schlenk, S. Kayser, L. Bullinger, et al. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood* **2014**, 124 (23), 3441–3449.
102. W. Zhang, M. Konopleva, Y.X. Shi, et al. Mutant FLT3: A direct target of sorafenib in acute myelogenous leukemia. *J. Natl. Cancer Inst.* **2008**, 100 (3), 184–198.
103. G. Borthakur, H. Kantarjian, F. Ravandi, et al. Phase I study of sorafenib in patients with refractory or relapsed acute leukemias. *Haematologica* **2011**, 96 (1), 62–68.
104. M. Crump, D. Hedley, S. Kamel-Reid, et al. A randomized phase i clinical and biologic study of two schedules of sorafenib in patients with myelodysplastic syndrome or acute myeloid leukemia: A NCIC (National Cancer Institute of Canada) Clinical Trials Group Study. *Leuk. Lymphoma* **2010**, 51 (2), 252–260.
105. F. Ravandi, M.L. Alattar, M.R. Grunwald, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood* **2013**, 121 (23), 4655–4662.
106. H. Serve, U. Brunnberg, O. Ottmann, et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: Results from a randomized, placebo-controlled trial. *J. Clin. Oncol.* **2013**, 31 (25), 3110–3118.
107. C. Röllig, H. Serve, A. Hüttmann, et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): A multicentre, phase 2, randomised controlled trial. *Lancet Oncol.* **2015**, 16 (16), 1691–1699.
108. T. Sato, X. Yang, S. Knapper, et al. FLT3 ligand impedes the efficacy of FLT3 inhibitors in vitro and in vivo. *Blood* **2011**, 117 (12), 3286–3293.
109. Y. Bin Chen, S. Li, A.A. Lane, et al. Phase i trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. *Biol. Blood Marrow Transplant.* **2014**, 20 (12), 2042–2048.
110. A. Antar, M.A. Kharfan-Dabaja, R. Mahfouz, A. Bazarbachi. Sorafenib maintenance appears safe and improves clinical outcomes in FLT3-ITD acute myeloid leukemia after allogeneic hematopoietic cell transplantation. *Clin. Lymphoma, Myeloma Leuk.* **2015**, 15 (5), 298–302.
111. S.K. MetzelDer, T. SchroeDer, A. Finck, et al. High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. *Leukemia* **2012**, 26 (11), 2353–2359.
112. T. Fischer, R.M. Stone, D.J. DeAngelo, et al. Phase IIB trial of oral midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. *J. Clin. Oncol.* **2010**, 28 (28), 4339–4345.
113. R.M. Stone, D.J. DeAngelo, V. Klimek, et al. Patients with acute myeloid leukemia and an activating mutation in FLT3 respond to a small-molecule FLT3 tyrosine kinase inhibitor, PKC412. *Blood* **2005**, 105 (1), 54–60.
114. B.W. Cooper, T.L. Kindwall-Keller, M.D. Craig, et al. A phase i study of midostaurin and azacitidine in relapsed and elderly AML patients. *Clin. Lymphoma, Myeloma Leuk.* **2015**, 15 (7), 428-432.e2.
115. P. Strati, H. Kantarjian, F. Ravandi, et al. Phase I/II trial of the combination of midostaurin (PKC412) and 5-azacytidine for patients with acute myeloid leukemia and myelodysplastic syndrome. *Am. J. Hematol.* **2015**, 90 (4), 276–281.
116. R.M. Stone, S.J. Mandrekar, B.L. Sanford, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N. Engl. J. Med* 377 (5), 454–464.
117. J.E. Cortes, H. Kantarjian, J.M. Foran, et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. *J. Clin. Oncol.* **2013**, 31 (29), 3681–3867.
118. M. Levis, F. Ravandi, E.S. Wang, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. *Blood* **2011**, 117 (12), 3294–3301.
119. M.J. Levis, A.E. Perl, H. Dombret, et al. Final Results of a Phase 2 Open-Label, Monotherapy Efficacy and Safety Study of Quizartinib (AC220) in Patients with FLT3-ITD Positive or Negative Relapsed/Refractory Acute Myeloid Leukemia After Second-Line Chemotherapy or Hematopoietic Stem Cell Transplantation. *Blood* **2012**, 120 (21), 673–673.
120. M. Swaminathan, H.M. Kantarjian, N. Daver, et al. The Combination of Quizartinib with Azacitidine or Low Dose Cytarabine Is Highly Active in Patients (Pts) with FLT3-ITD Mutated Myeloid Leukemias: Interim Report of a Phase I/II Trial. *Blood* **2017**, 130 (Suppl_1), 723–723.
121. E.A. Lasater, K.C. Lin, Q. Wang, et al. Crenolanib is a selective type i pan-FLT3 inhibitor Catherine Choy Smith1,2. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, 111 (14), 5319–5324.
122. J.K. Randhawa, H. Kantarjian, G. Borthakur, et al. 57th Annual Meeting & Exposition. Results of a phase II study of crenolanib in relapsed/refractory acute myeloid leukemia patients (Pts) with activating FLT3mutations. *Am. Soc. Hematol.*
123. J. Zhou, C. Bi, J. V. Janakakumara, et al. Enhanced activation of STAT pathways and overexpression of survivin confer resistance to FLT3

inhibitors and could be therapeutic targets in AML. *Blood* **2009**, 113 (17), 4052–4062.
124. M.S. Redell, M.J. Ruiz, T.A. Alonzo, R.B. Gerbing, D.J. Tweardy. Stat3 signaling in acute myeloid leukemia: Ligand-dependent and -independent activation and induction of apoptosis by a novel small-molecule Stat3 inhibitor. *Blood* **2011**, 117 (21), 5701–5709.
125. M.J. Krueger, M. Minus, W. Liu, et al. A Novel STAT3 Inhibitor Has Potent Activity in Preclinical Models of Acute Myeloid Leukemia That Incorporate the Stromal Environment. *Blood* **2015**, 126 (23), 569–569.
126. D.Y. Oh, S.H. Lee, S.W. Han, et al. Phase I study of OPB-31121, an oral STAT3 inhibitor, in patients with advanced solid tumors. *Cancer Res. Treat.* **2015**, 47 (4), 607–615.
127. F. Hayakawa, K. Sugimoto, Y. Harada, et al. A novel STAT inhibitor, OPB-31121, has a significant antitumor effect on leukemia with STAT-addictive oncokinases. *Blood Cancer J.* **2013**, 3 (11), 166.
128. F. Wang, J. Travins, B. DeLaBarre, et al. Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. *Science (80).* 340, 622–626.
129. K. Yen, F. Wang, J. Travins, et al. AG-221 Offers a Survival Advantage In a Primary Human IDH2 Mutant AML Xenograft Model. In *Blood*; San Diego, CA, **2013**; Vol. 122, pp 240–240.
130. E. Stein, M. Tallman, D.A. Pollyea, et al. Abstract CT103: Clinical safety and activity in a phase I trial of AG-221, a first in class, potent inhibitor of the IDH2-mutant protein, in patients with IDH2 mutant positive advanced hematologic malignancies. *Cancer Res.* **2014**, 74 (19_Supplement), CT103–CT103.
131. A.K. Burnett, N.H. Russell, A.E. Hunter, et al. Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival. *Blood* **2013**, 122 (8), 1384–1394.
132. H.M. Kantarjian, H.P. Erba, D. Claxton, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. *J. Clin. Oncol.* **2010**, 28 (4), 549–555.
133. B.S. Chhikara, K. Parang. Development of cytarabine prodrugs and delivery systems for leukemia treatment. *Expert Opin. Drug Deliv.* **2010**, 7 (12), 1399–1414.
134. S. Faderl, M. Wetzler, D. Rizzieri, et al. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: Results from the CLASSIC I trial. *J. Clin. Oncol.* **2012**, 30 (20), 2492–2499.
135. T.M. Kadia, S. Faderl, F. Ravandi, et al. Final results of a phase 2 trial of clofarabine and low-dose cytarabine alternating with decitabine in older patients with newly diagnosed acute myeloid leukemia. *Cancer* **2015**, 121 (14), 2375–2382.
136. A. Nazha, H. Kantarjian, F. Ravandi, et al. Clofarabine, idarubicin, and cytarabine (CIA) as frontline therapy for patients ≤60 years with newly diagnosed acute myeloid leukemia. *Am. J. Hematol.* **2013**, 88 (11), 961–966.
137. J.M. Middeke, R. Herbst, S. Parmentier, et al. Clofarabine salvage therapy before allogeneic hematopoietic stem cell transplantation in patients with relapsed or refractory AML: Results of the BRIDGE trial. *Leukemia* **2016**, 30 (2), 261–267.
138. K. Barbosa, A.J. Deshpande. Therapeutic targeting of leukemia stem cells in acute myeloid leukemia. *Front. Oncol.* **2023**, 13, 1204895.
139. S.K. Sharma, D. Choudhary, D. Doval, et al. Hematopoietic Stem Cell Transplant for Hematological Malignancies: Experience from a Tertiary Care Center in Northern India and Review of Indian Data. *South Asian J. Cancer* **2022**, 11 (01), 062–067.
140. J.P. Bewersdorf, R.M. Shallis, A. Derkach, et al. Efficacy of FLT3 and IDH1/2 inhibitors in patients with acute myeloid leukemia previously treated with venetoclax. *Leuk. Res.* **2022**, 122, 106942.
141. Y. Numan, Z. Abdel Rahman, J. Grenet, et al. Gilteritinib clinical activity in relapsed/refractory FLT3 mutated acute myeloid leukemia previously treated with FLT3 inhibitors. *Am. J. Hematol.* **2022**, 97 (3), 322–328.
142. J.P. Bewersdorf, R.M. Shallis, A. Derkach, et al. Venetoclax-based salvage therapy in patients with relapsed/refractory acute myeloid leukemia previously treated with FLT3 or IDH1/2 inhibitors. *Leuk. Lymphoma* **2023**, 64 (1), 188–196.
143. H. Bolouri, J.E. Farrar, T. Triche, et al. The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. *Nat. Med.* **2018**, 24 (1), 103–112.
144. G. Cengiz Seval, M. Ozcan. Treatment of acute myeloid leukemia in adolescent and young adult patients. *J. Clin. Med.* **2015**, 4 (3), 441–459.
145. K. Hajian-Tilaki. Receiver operating characteristic (ROC) curve analysis for medical diagnostic test evaluation. *Casp. J. Intern. Med.* **2013**, 4 (2), 627–635.
146. B. Avni, M. Koren Michowitz. Myeloid sarcoma: Current approach and therapeutic options. *Ther. Adv. Hematol.* **2011**, 2 (5), 309–316.
147. B.S. Chhikara, D. Mandal, K. Parang. Synthesis and evaluation of fatty acyl ester derivatives of cytarabine as anti-leukemia agents. *Eur. J. Med. Chem.* **2010**, 45 (10), 4601–4608.
148. S.Z. Berisha, S. Shetty, T.W. Prior, A.L. Mitchell. Cytogenetic and molecular diagnostic testing associated with prenatal and postnatal birth defects. *Birth Defects Res.* **2020**, 112 (4), 293–306.
149. U. Creutzig, M.M. Van Den Heuvel-Eibrink, B. Gibson, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: Recommendations from an international expert panel. *Blood* **2012**, 120 (16), 3167–3205.
150. H. Zhao, Z. Dong, D. Wan, et al. Clinical characteristics, treatment, and prognosis of 118 cases of myeloid sarcoma. *Sci. Rep.* **2022**, 12 (1), 6752.
151. M. Kumar, F. Sonia, S.M. Hamadani, S.A. Abbas. A rare case of acute cord compression from spinal myeloid sarcoma: a complication of Acute Myeloid Leukemia. *Cureus* **2020**, 2 (8), 9502.
152. M. Samborska, M. Barańska, J. Wachowiak, et al. Clinical characteristics and treatment outcomes of myeloid sarcoma in children: the experience of the Polish Pediatric Leukemia and Lymphoma Study Group. *Front. Oncol.* **2022**, 12, 935373.
153. S.R. Jones, A. Rahrig, A.J. Saraf. Leukapheresis in Pediatric Acute Leukemia with Hyperleukocytosis: A Single-Center Experience. *Children*. 2022, p 503.
154. C. Ganzel, J.W. Lee, H.F. Fernandez, et al. CNS involvement in AML at diagnosis is rare and does not affect response or survival: data from 11 ECOG-ACRIN trials. *Blood Adv.* **2021**, 5 (22), 4560–4568.
155. D. Deak, N. Gorcea-Andronic, V. Sas, et al. A narrative review of central nervous system involvement in acute leukemias. *Ann. Transl. Med.* **2021**, 9 (1), 68–68.
156. L. Bai, Y. zhan Zhang, C. hua Yan, et al. Outcomes of allogeneic haematopoietic stem cell transplantation for paediatric patients with MLL-rearranged acute myeloid leukaemia. *BMC Cancer* **2022**, 22 (1), 896.
157. P. Wang, Z. Yang, M. Shan, et al. Maternal and Fetal Outcomes of Acute Leukemia in Pregnancy: A Retrospective Study of 52 Patients. *Front. Oncol.* **2021**, 11, 803994.
158. J. Ding, Y.H. Xiao, J. Fu, et al. Pregnancy and neonatal outcomes in 25 pregnant women diagnosed with new-onset acute myeloid leukemia during pregnancy. *Arch. Gynecol. Obstet.* **2024**, 310 (2), 783–791.
159. D. Milojkovic, J.F. Apperley. How I treat leukemia during pregnancy; *Blood*. **2014,** 123(7), 974–984.
160. I.D. Kouchkovsky, M. Abdul-Hay. Acute myeloid leukemia: a comprehensive review and 2016 update; *Blood Cancer J.* **2016,** 6(7), e441.
161. K. Adhikary, S. Mohanty, B. Bandyopadhyay, R. Maiti, J.K. Bhattacharya, P. Karak. β-Amyloid peptide modulates peripheral immune responses and neuroinflammation in rats. *Biomol. Concepts.* **2024**, 15(1), 2022-0042.
162. C.W. Elgarten, R. Aplenc. Pediatric acute myeloid leukemia: updates on biology, risk stratification, and therapy. *Curr. Opin. Pediatr*. **2020**, 32 (1), 57–66.

163. Y.W. Li, Y.F. Xu, W. Hu, S.X. Qian, C. Chen. Acute myeloid leukemia during pregnancy: a single institutional experience with 17 patients and literature review. *Int. J. Hematol.* **2020**, 112 (4), 487–495.
164. T. Mukherjee, S. Mohanty, J. Kaur, et al. Exploring small-molecule inhibitors targeting MAPK pathway components: Focus on ERK, MEK1, and MEK2 kinases in cancer treatment. *Chem. Biol. Lett.* **2024**, 11 (2), 659.
165. Y. Pei, Y. Gou, N. Li, X. Yang, X. Han, H. Huiling. Efficacy and safety of platinum-based chemotherapy for ovarian cancer during pregnancy: a systematic review and meta-analysis. *Oncol. Ther.* **2022**, 10 (1), 55–73.
166. X. Jiang, Z. Ye, W. Yu, Q. Fang, Y. Jiang. Chemotherapy for ovarian cancer during pregnancy: A systematic review and meta-analysis of case reports and series. *J. Obstet. Gynaecol. Res.* **2021**, 47 (10), 3425–3436.
167. A. Chang, S. Patel. Treatment of acute myeloid leukemia during pregnancy. *Ann. Pharmacother.* **2015**, 49 (1), 48–68.
168. T.W. LeBlanc, L.J. Fish, C.T. Bloom, A. El-Jawahri, D.M. Davis, S.C. Locke, K.E. Steinhauser, K.I. Pollak. Patient experiences of acute myeloid leukemia: A qualitative study about diagnosis, illness understanding, and treatment decision-making. *Psychooncology* **2017**, 26 (12), 2063–2068.
169. S. Franco, X. Geng, V. Korostyshevskiy, J.E. Karp, C. Lai. Systematic review and meta-analysis: Prognostic impact of time from diagnosis to treatment in patients with acute myeloid leukemia. *Cancer* **2023**, 129 (19), 2975–2985.
170. Y. Guo, W. Wang, H. Sun. A systematic review and meta-analysis on the risk factors of acute myeloid leukemia. *Transl. Cancer Res.* **2022**, 11 (4), 796–804.
171. F. Altaf, Z. Qureshi, A. Jamil, R. Siddique. AML-356 Meta-Analysis of Therapeutic Approaches in Acute Myeloid Leukemia: Unveiling Trends and Predictors of Treatment Response. *Clin. Lymphoma Myeloma Leuk.* **2024**, 24, S309.
172. J. Zhu, J. Fan, T. Xie, et al. Venetoclax combined chemotherapy versus chemotherapy alone for acute myeloid leukemia: a systematic review and meta-analysis. *Front. Oncol.* **2024**, 14, 14.
173. E. Kimby, P. Nygren, B. Glimelius, S.B.U.-group. Swedish Council of Technology Assessment in Health Care. A systematic overview of chemotherapy effects in acute myeloid leukaemia. *Acta Oncol* 40 (2–3), 231–252.
174. M. Shahzad, S.G. Chaudhary, E. Tariq, et al. Use of endpoints in phase III randomized controlled trials for acute myeloid leukemia over the last 15 years: a systematic review. *Leuk. Lymphoma* **2023**, 64 (2), 273–282.
175. S. Miyawaki, H. Sakamaki, S. Ohtake, et al. A randomized, postremission comparison of four courses of standard-dose consolidation therapy without maintenance therapy versus three courses of standard-dose consolidation with maintenance therapy in adults with acute myeloid leukemia: The Japan Adult Leukemia Study Group AML97 study. *Cancer* **2005**, 104 (12), 2726–2734.
176. A. Rashidi, R.B. Walter, M.S. Tallman, F.R. Appelbaum, J.F. DiPersio. Maintenance therapy in acute myeloid leukemia: An evidence-based review of randomized trials. *Blood* **2016**, 128 (6), 763–773.
177. X. Li, H.S. Suh, J. Lachaine, et al. Comparative efficacy of venetoclax-based combination therapies and other therapies in treatment-naive patients with acute myeloid leukemia ineligible for intensive chemotherapy: a network meta-analysis. *Value Heal.* **2023**, 26 (12), 1689–1696.
178. D.R. Richardson, C.J. Mhina, R. Teal, A.C. Cole, K. Adapa, A.L. Bryant, N. Crossnohere, S.C. Wheeler, J.F.P. Bridges, W.A. Wood. Experiences of treatment decision-making among older newly diagnosed adults with acute myeloid leukemia: a qualitative descriptive study. *Support Care Cancer.* **2024**, 32 (3), 197.

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