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NOVEL DRUG DISCOVERY AND DESIGN IN ACUTE MYELOID LEUKEMIA

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ABSTRACT

Acute myeloid leukemia (AML) is a complex hematological disease characterized by genetic and clinical heterogeneity. Numerous previous studies have shown that acute myeloid leukemia (AML) patients under the age of 60 have around a 50% survival rate, while older patients have a worse prognosis, with around 15% survival. Poor treatment outcomes are often due to primary chemotherapy resistance and high relapse rates, emphasizing that standard chemotherapy is insufficient to cure most AML patients. More recently, many innovative approaches to drug design have been proposed, and drugs targeting the FMS-like tyrosine kinase 3 (FLT3) mutation or the iso-citrate dehydrogenase (IDH)-1 or -2 mutation have demonstrated significantly improved outcomes for AML patients. Targeted delivery of nanomedicines offers potential strategies to improve the efficacy of molecular drugs. In this review, we will present and describe these recently approved drugs as well as selected novel agents against AML that are currently under investigation, and show the most promising results as monotherapy or in combination with chemotherapy. The World Health Organization (WHO) defines palliative care as an approach that can improve the quality of life (QoL) of patients and their families through the timely identification of deteriorating health, holistic assessment of needs, management of pain and other symptoms (physical, psychosocial, and spiritual), and the proposal of a person-centered planning of care .However, the modern management of AML has been significantly improved by the availability of novel targeted agents as well as drugs with novel cytotoxic delivery approaches. Besides conventional treatments and new therapeutic strategies, palliative medication should also be taken into account for the optimal management of AML patients.

KEYWORDS: Acute myeloid leukemia, hematologic malignancies, drug delivery, drug treatment, nanomedicines.

INTRODUCTION

Acute myeloid leukemia (AML) is a malignant disorder characterized by an impaired differentiation of hematopoietic stem cells, leading to an abnormal accumulation of immature malignant cells and the reduced production of healthy mature blood cells.[1] Among leukemias, AML is one of the most common diseases, accounting for approximately 30% of leukemia adult cases.[2] AML is primarily a disease of later adulthood: the incidence rate by age increases from 50 years, reaching the peak at around 80 years of age, and the median age at diagnosis is 65 years.[3,4] With an incidence rate that has increased over the past two decades by 30%,[5] AML represents a substantial health problem that requires strict monitoring and innovative treatment strategies. Leukemia encompasses a set of malignant conditions that affect blood and blood forming tissues. Normal blood cells are derived from hematopoietic progenitor cells, which go on to differentiate into cells of either myeloid or lymphoid lineage. Myeloid cells become erythrocytes, platelets, myeloblasts, and granulocytes, while lymphoid cells develop into lymphoblasts that subsequently differentiate into B-lymphocytes, T-lymphocytes or natural killer cells. In leukemia, normal hematopoiesis is suppressed by the uncontrolled proliferation and accumulation of leukemic cells. Leukemias are classified by the types of cells affected and are further defined by the developmental stage of the originating cells.[4] They are grouped into four major categories: acute myeloid (AML) and acute lymphoblastic leukemia (ALL), and chronic myeloid (CML), and chronic lymphoblastic leukemia (CLL). Myeloid leukemias are derived from myeloblasts and lymphoblastic leukemias are derived from lymphoblasts, acute conditions arise from early, immature cells and chronic conditions are derived from mature, abnormal cells. Leukemia is generally considered an uncommon condition. In the United States in 2019, there were estimated to be approximately 1.76 million new cases of cancer diagnosed in the overall population with 61,780 being leukemia. Approximately

9% of newly diagnosed cases of leukemia are in children and young adults. Acute leukemias are the most common type and are responsible for approximately one third of all cancers in this age group. Mixed lineage leukemias (MLL) are a subtype of acute disease and have features of both AML and ALL. Chronic leukemias are very rare in children.[5]

Identification of early drugs used to treat leukemia was not target driven. These compounds were, instead, already in use for various other diseases and disorders and were administered to patients in the hope of providing a path to recovery. Arsenic was the first recognized leukemia therapy and was a principal component in a potassium bicarbonate based solution of arsenic trioxide, developed in the late Eighteenth century by Thomas Fowler and first used as a leukemia treatment in 1865. Arsenic containing compounds, with or without concomitant radiation, remained the standard therapy for leukemia up until the introduction of busulphan in 1953. L-asparaginase, an enzyme that catalyzes the conversion of L-asparagine to L-aspartic acid and ammonia, has been used to treat pediatric patients with ALL since the mid-1960s. In the first account of clinical use, Dolowy et al. showed that an 8 year-old child achieved a partial response upon treatment with this enzyme. Hill et al., subsequently reported that patients treated with L-asparaginase had significant improvement, even with advanced disease, and achieved complete remission in one of three patients tested. Clinical trials followed, which further demonstrated the efficacy of such a targeted treatment as both a stand-alone therapy and in combination with other pharmaceutical agents. But it was not until recently that it was found that a cytogenetic and molecular subgroup of AML characterized by chromosome 7 monosomy could also benefit from L-asparaginase treatment, a treatment that may preferentially target leukemia stem cells in the bone marrow microenvironment.[6]

In addition to the development of new drug treatment strategies, radiation therapy became part of the conventional methods used to treat leukemic disease. Since then, treatment options for leukemia have evolved, from technological advances such as stem cell transplants, to the development of new targeted therapies based on the increased understanding of molecular events leading to leukemia, to taking advantage of a patient's own immune system in immunotherapy. In this review, we will give an overview of disease subtypes, etiology and current treatment options. We will discuss the more recent understanding of the influence of the tumor microenvironment within the bone marrow on cancer stem cell proliferation and its impact on drug resistance. Lastly, we will address the challenges this poses for traditional drug discovery efforts and how new phenotypic 3D screening methods that can more closely mimic such a tumor microenvironment may help to overcome these limitations.[7]

Etiology of Acute Myeloid Leukemias

Leukemias are thought to arise from a single mutant cell, but the cancer populations are not clonal. Several mutations are possible within the spectrum of an individual patient's disease. In accordance with Knudson's two-hit hypothesis, leukemias are cancers that are generally caused by two oncogenic events. Knudson's hypothesis, although ground-breaking for its time, does have some limitations because it is now known that several tumor suppressor genes (TSGs) do not fit within its confines. In an effort to expand and redefine this paradigm, Paige placed these TSGs into three main categories, including those that arise from (a) monoallelic disruption (haploinsufficiency, dominant negative and gain-of function isoforms); (b) multiple gene interactions (multi-step tumorigenesis, genetic modifiers or mutators); and (c) dual function TSGs that have both tumor-suppressing and tumor-promoting properties.[8] Oncogenic events include deviant expression of proto-oncogenes, and chromosomal abnormalities that result in changes in chromosome number, chromosome inversions, or creation of translocations leading to gene fusions and subsequent modification(s) of cell signaling pathways due to over or under activity of kinases and/or transcription factors. A subset of AML, referred to as t- or therapy related-AML are, as the name suggests, caused by mutations that arise as a result of treatments for other disease conditions, including benign and malignant neoplasms and immune system disorders. Prior disease management may include individual or combined treatments including chemotherapy, radiation, and immunosuppressive therapies. Prognosis for patients with t-AML is generally very poor; supportive therapy is most often the only treatment option.[9] Irregularities at the *Mixed Lineage Leukemia* gene (*MLL*) locus present on 11q23 are frequently responsible for aggressive cancers that most often occur in the pediatric population and are due to conversion of *MLL* into an active oncogenic state. MLL has been shown to fuse with many partners including the Acute Lymphoblastic Leukemia 1-Fused Gene from Chromosome 4 (AF4), Acute Lymphoblastic Leukemia 1-Fused Gene from Chromosome 6 (AF6), Acute Lymphoblastic Leukemia 1-Fused Gene from Chromosome 9 (AF9), Acute Lymphoblastic Leukemia-1 Fused Gene from Chromosome 10 (AF10), Eleven-Nineteen-Leukemia (ENL), Eleven-Nineteen Lysine-rich Leukemia (ELL), CREB [cAMP (cyclic adenosine monophosphate) Response Element Binding] Binding Protein (CBP), Protein 300 (P300), ALL 1 [Acute Lymphoblastic Leukemia 1]-Fused Gene from Chromosome 1 Protein (AF1p), Growth Arrest Specific Protein 7 (GAS7), Abl-Interactor 1 (ABI1), and Extra Eleven-Nineteen Leukemia (EEN) proteins[10] Alcalay et al. showed that some fusion proteins in AML induced a mutator phenotype, down regulating the activity of DNA base excision repair genes. Hence, the presence of fusion proteins impaired DNA repair mechanisms leading to further DNA damage and induction of a leukemic phenotype. The NUP98-NSD1 fusion protein occurs in

4.4% of pediatric AML and is associated with a <10% event-free 4-year survival rate. NUP98, or Nucleoporin 98-kDa, is located on chromosome 11p15, and is part of the nuclear pore complex, which controls movement of protein and RNA between the nucleus and the cytoplasm. Chromosomal rearrangements are responsible for fusion of NUP98 with several different partner genes which may, broadly, be grouped into three categories: homeodomain; nuclear nonhomeotic, which includes NSD1; and cytoplasmic. NSD1, or Nuclear Receptor-binding SET [Su(var)3-9, Enhancer-of-zeste and Trithorax] Domain Protein 1, is located on chromosome 5q35 and is a histone methyltransferase . NSD1 predominantly dimethylates lysine 36, located close to the globular domain of nucleosomal histone H3. NSD1 retains methyltransferase activity in the fusion, and it is this property that is essential for leukemia progression.[11] Aberrant expression of NUP98-NSD1 promotes leukemogenesis by activating transcription of hematopoietic regulatory genes, principally *Homeobox A* (*HOXA*), *Homeobox B* (*HOXB*), and *Myeloid Ecotropic Viral Integration Site 1 Homolog* (*MEIS1*), which subsequently activate down-stream proto-oncogenic target gene *Myeloblastosis Viral Oncogene Homolog* (*c-Myb*). *HOX* expression is markedly reduced as myeloblasts differentiate into mature hematopoietic cells. When *HOX* expression is continually stimulated, myeloblastic cells become self-renewing and fail to differentiate, thus exhibiting a stem cell-like, immortal phenotype that most often leads to cancer. Secondary events leading to leukemogenesis include activating mutations in additional proto-oncogenes such as the NOTCH1 transmembrane receptor, implicated specifically in T-cell derived ALL.[12] Mutations in the receptor tyrosine kinase FMS [Feline McDonough Sarcoma] Related Tyrosine Kinase 3, FLT3] are often due to internal tandem duplications, referred to as FLT3 ITD or due to point mutations in the tyrosine kinase domain in the codon for an aspartate (D835) or an isoleucine (I836) residue, collectively termed FLT3 TKD. Loss-of-function mutations in tumor-suppressor genes such as Retinoblastoma protein, pRb, and p53 have been described as well and mutations in non-coding regions of DNA have also been implicated in malignant transformation.[13]

Treatment / Management

Individuals who achieve complete remission (CR) with a blast count of less than 5% in the bone marrow after induction therapy tend to have increased survival. Despite induction therapy, there is still minimal residual disease for which consolidation therapy is initiated to prevent any risk of relapse by eliminating the residual disease. Despite many advances, the mainstay of therapy remains a combination of cytarabine-based and anthracycline-based regimens. For eligible candidates, allogeneic stem cell transplantation should be considered.[14] Monoclonal antibodies specifically target antigens expressed on the surface of leukemic cells; they promote anti-neoplastic activity by immunomodulating the tumor microenvironment, by exerting cell-mediated cytotoxicity, or by delivering conjugated potent chemotherapy to tumor cells. In recent years, a variety of antigen-specific immunotherapies, including antibodies against leukemic myeloblast antigens (CD33, CD123) and the leukemia stem cell markers (CD123, CD25, CD44, CD96, CD47, CD32) have been developed and tested in preclinical studies.[9,10] However, these first generation antibodies that were generated to directly target leukemic cells showed limited anti-tumor activities. A phase II/III study of the anti-CD123 antibody talacotuzumab (JNJ-56022473), in association with decitabine, in patients with AML who are not candidates for intensive chemotherapy, has been recently completed, and results will be available soon.[15]

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are metabolic enzymes located in the cytoplasm/ peroxysomes and mitochondria, respectively that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate. Point mutations in these proteins have been found to be associated with several malignancies, including AML. In particular, IDH1 and IDH2 mutations account for 20% of all AML cases, affecting 7–14% and 8–19% of patients, respectively. In vitro and in vivo studies proved that mutations in IDH proteins decrease their enzymatic activity as well as confer a gain of function activity to convert α-ketoglutarate to D-2-hydroxyglutarate (D-2HG). D-2HG and α-KG share similar structures; therefore, D-2HG can act as a competitive inhibitor of the other metabolite, interfering with α-KG activities such as cellular metabolism and epigenetic regulation. The dysregulation induced by α-KG translates in an arrest of cell differentiation, and thus oncogenesis. Novel therapeutic approaches have been developed to target leukemic cells carrying IDH1/2 mutations (AG-120, AG-221, BAY1436032, IDH305, AG-881, FT-2102).[16] The specific inhibitor of IDH1, ivosidenib (AG-120), was evaluated for the first time in a clinical trial as a single agent in patients with IDH mutation-positive advanced hematologic malignancies. Doses ranged from 300 mg to 1200 mg once daily, with a subgroup of patients that received the dosage of 100 mg twice per day. All ivosidenib doses tested in the pharmacokinetic/pharmacodynamic analysis were able to reduce the D-2HG plasma level. The maximum tolerated dose was not defined, and the most common grade ≥3 AEs (≥15%) were febrile neutropenia, anemia, leukocytosis, and pneumonia. Among 78 patients with evaluable response, 30 patients experienced an ORR (38.5%) and 14 patients (17.9%) experienced a CR. A variant allele frequency (VAF) analysis using next-generation sequencing (NGS) demonstrated that ivosidenib treatment resulted in a clearance of mutant IDH1 in 27.3% of patients with CR. In a recent phase I study, CR, CR + CRi, and ORR were observed, respectively, in 21.6%, 30.4%, and 41.6% of patients with IDH1-mutated AML receiving ivosidenib 500-mg monotherapy, with a median duration of 8.2 months, 9.3 months, and 6.5 months.[17] Enasidenib (AG-221) is an

oral, selective inhibitor of mutant IDH2 that presented an acceptable tolerability profile, with 41% of 239 AML patients (113 in the dose-escalation phase and 126 in the four-arm expansion phase) reporting grade 3–4 treatment-emergent adverse events (hyperbilirubinemia, 12%; IDH differentiation syndrome, 6%; thrombocytopenia, 6%), in a first-in-human, phase 1/2 study . Besides the safety and tolerability, this trial also evaluated the pharmacokinetic and pharmacodynamic characteristics of enasidenib in an expansion phase (dose of 100 mg once daily), showing clinical efficacy. Among 176 patients (74%) with relapsed/refractory disease and IDH2 mutation, 40.3% achieved an ORR and 19.3% achieved CR.[18] The median OS was 9.3 months in all of the relapsed/refractory patients, and 19.7 months in those patients with relapsed/refractory disease who reached a CR. Based on these promising data, enasidenib was recently approved by the FDA in advanced mutant IDH2 AML. The multicenter, open-label, randomized, phase III study IDHENTIFY is currently recruiting elderly subjects (≥60 years) with IDH2 mutant AML to compare enasidenib treatment to conventional care regimens.[19]

Induction Therapy

This is a standard of care for younger patients, elderly with a low risk of treatment-related mortality (TRM), and ones with favorable and intermediate-risk factors. The induction therapy is highly toxic to bone marrow, causing pancytopenias and bleeding complications, gastrointestinal system issues, kidney failure due to tumor lysis syndrome, and electrolyte disturbances. It may take up to 1 month for the cell counts to recover, and these patients need aggressive monitoring to manage any complications. Baseline cardiac function should be estimated before initiating the treatment, and the ejection fraction (EF) needs to be monitored carefully, as anthracyclines can cause significant cardiotoxicity.[20] Studies have shown greater benefit with higher doses, but toxicities may limit its use. It consists of the "7+3" regimen that includes continuous infusion of cytarabine for seven days along with anthracycline on days 1 to 3. Patients with refractory disease have shown higher CR and similar overall survival (OS) by using higher doses of cytarabine or by using a combination of fludarabine, cytarabine, and idarubicin. Despite TRM in older patients, chemotherapy has shown to improve the survival rate among the elderly (older than 65 years).[21] Decitabine, a methylating agent used in the treatment of MDS, has shown improvement in OS in the elderly population. The response should be evaluated by repeating the bone marrow aspirate and biopsy after 2 weeks of initiating the induction therapy. Reinduction can be done with high dose cytarabine or by combining with etoposide if there is persistent evidence of disease. About 60% to 80% de novo AML will achieve CR with induction therapy. Even before the diagnosis, if APL is suspected, then the treatment should be initiated with all-trans retinoic acid (ATRA), as early use of ATRA decreases the risk of disseminated intravascular coagulation (DIC) and mortality associated with it.[22]

Consolidation Therapy

After achieving CR with induction therapy, consolidation therapy is initiated with high dose cytarabine, called HiDAC, and hematopoietic cell transplantation (HCT). HCT is preferred in individuals less than 60 years of age with intermediate or unfavorable prognoses. If a donor is available, then allogeneic HCT is preferred over autologous HCT. They should be monitored for signs or symptoms of acute or chronic graft versus host disease (GVHD).[22]

Novel Targets

Ongoing studies with Fms-like tyrosine kinase 3 (FLT3) inhibitors, IDH inhibitors, and immune therapies. All blood products must be irradiated to prevent transfusion-related graft versus host disease, which is usually fatal. IV antibiotics are given to febrile patients, and prophylactic antifungal therapy is recommended.[23]

Novel Targeted Therapies in Development

The advent of new technological approaches in recent years has helped unravel the complexity of AML. Genomic approaches, including single-cell RNA sequencing, CRISPR gene editing, multi-targeted tissue imaging studies, and several other technological advances, have provided a better understanding of the complex genomic landscape of this disease. These recent developments have produced key discoveries in developing small molecular drugs that can potentially target specific genetic abnormalities or mutant proteins in AML. These targeted drugs can be used in conjunction with chemotherapy or in cases when chemotherapy is not effective. In addition, novel targeted drugs were recently developed that have shown promising results against leukemic clone variations.[24] The identification of specific molecular targets for an individual's cancer requires careful examination to determine correct and exact targets for use. These targeted molecular therapies can be advantageous, as they have the potential to cause less damage to normal cells, with fewer overall side effects. One such targeted drug is the class of menin inhibitors for *KMT2A*-rearranged AML.

Menin Inhibitors

The rearrangement of *KMT2A* (MLL1) occurs in up to 10% of acute leukemias and is especially common in infant leukemia, with an occurrence rate of at up to 80%.[25] Menin inhibitor treatment disrupts the interactions between menin and *KMT2A*. The transcriptional regulator *KMT2A* contains binding domains for menin, where it forms the menin-KMT2A-LEDGF complex by menin binding to menin binding domains (MBDs). This complex links *KMT2A* to chromatin, and the menin-KMT2A complex plays a crucial role in the regulation of HOX genes of hematopoiesis, specifically the leukemogenic HOXA9 and MEIS1 co-factor in myeloid progenitor stem cells.[25] In *KMT2A* rearrangement (*KMT2Ar*), this AML-sustaining fusion protein occurs and causes the overexpression of HOXA9/MEIS1. *KMT2Ar* AML

carries a poor prognosis and is associated with a higher relapse rate. As a cofactor, menin is necessary for *KMT2A* to bind to HOX gene promoters, and this fact has pushed the development of KMT2A-menin interaction-targeting small molecule inhibitors. Notably, menin inhibitors may be beneficial for the treatment of overexpression of other HOX genes in other subtypes of leukemia.

Menin inhibitors currently undergoing clinical trials include SNDX-5613 and KO-539, among others. The SNDX-5613 phase 1 study enrolled both adult and pediatric patients with relapsed or refractory acute leukemia, with a focus on patients with *KMT2Ar* or *NPM1*-mutated AML.[24] SNDX-5613 has been generally well tolerated thus far, with the most common side effects including QTc prolongation, nausea, and diarrhea.[26] These trials continue to accumulate data, and whether some adverse events are class effects or related to individual compounds remains to be seen.

Tumor Suppressor Targets

The *TP53* tumor suppressor gene is frequently inactivated in cancers by loss-of-function or missense DNA binding domain mutations, seen in almost 50% of tumors in up to 15% of overall AML cases, and in 25% of elderly cases. These mutations can include loss of function or lead to protein unfolding and loss of DNA binding via substitutions of amino acid residues important for the structure of the core domain, specifically the ones making direct contact with the DNA.[21] It gets converted to methylene quinuclidinone (MQ), a reactive electrophile that covalently binds to the p53 core domain, and presumably, cysteine 277 is an ideal target for MQ to bind on p53. APR-246 also increases oxidative stress and induces ferroptosis as part of its anti-cancer mechanism of action.[27]

APR-246 has been tested in two clinical trials, in combination with azacitidine, showing synergistic cytotoxicity in the AML cell lines with *TP53* mutations, as well as in vivo models. Of the 100 patients across the two clinical trials, there was an overall response rate of 69% and a complete remission rate of 43%. The phase 3 trial comparing APR-246 with azacitidine compared to azacitidine alone has been completed, but is still under evaluation, and has not been published as of this date.

MCL-1 Inhibitors

MCL-1, as a member of the BCL-2 family of proteins, is a pro-survival regulator of apoptosis. Proteins in this family bind to pro-apoptotic BH-3-only activators, bestowing MCL-1 with a role in cell death avoidance. Hematological malignancies were shown to be dependent, not only on MCL-1, but on BCL-2 as well .[28] Development of MCL-1 inhibitors can be approached indirectly; for example, CDK inhibitors lead to decreased transcription of *MCL-1*, while mTOR inhibitors block MCL-1 translation . Multiple MCL-1 inhibitors have entered the clinical trial phase, including but not limited to AZD5991 and S64315. The macrocyclic molecule AZD5991 is selective for MCL-1 and acts in a mitochondria-dependent manner, highly specific at a cellular level for MCL-1. AZD5991 binds to MCL-1 directly at the ligand-binding pocket, inducing cell death and reducing MCL-1 levels. S63845 is another selective molecule that inhibits MCL-1. It binds with high specificity to the BH3-binding groove of MCL-1, where it activates the BAX/BAK-dependent apoptotic pathway.

XPO1 Inhibitors

Eltanexor (KPT-8602) is a second-generation inhibitor of XPO1-mediated nuclear export. This compound covalently binds to cysteine 528 in *XPO1*'s cargo-binding groove, blocking the interaction of *XPO1* with any cargo, therefore inhibiting nuclear export. Compared to the first-generation XPO1 inhibitor selinexor, eltanexor has a much lower penetration across the blood-brain barrier. Moreover, in a recently concluded study, *XPO1* inhibition via selinexor has shown promising results in hematological malignancies in in vitro and in vivo studies. Hence, these studies have confirmed that XPO1 inhibitors have a potential use as therapies for providing better remedies for AML patients.[29]

Immune Checkpoint Inhibitors

In recent years, immune checkpoint inhibitors have shown promising results in various cancers, and they are becoming a strong option in the targeting of cancer cells. For example, programmed cell death protein 1 (PD-1) and its ligands PD-L1 and PD-L2 are revolutionizing cancer treatment in lung cancer, melanoma, Hodgkin's lymphoma, and several other forms of cancer. Another immune blockade T-lymphocyte-associated protein 4 (CTLA-4) antibody was used in hematologic malignancies, showing promising results.[29] There was a significant increase in the survival rates using immune checkpoint inhibitor treatment, which provided justification for exploring clinical trials in order to bring better cures for AML patients. There is another potential option to use these immune checkpoint inhibitors in combination with other classes of inhibitors to tackle the complexity of this cancer. So far, only a single clinical study has been published regarding the use of a checkpoint inhibitor as a monotherapy for AML patients. This study included eight AML patients, along with another ten patients with different hematologic malignancies that were treated with the anti-PD-1 antibody pidilizumab within a phase I study. A full review of immunotherapy in AML is beyond the scope of this review, which focuses on targeted therapies, but the potential to combine targeted therapies and immunotherapies makes these relevant to mention.

Combinatorial Therapies in Development

To improve upon single agent therapies, a combinatorial approach seeks an advantage to strategically treat AML patients by targeting parallel pathways or providing

synergistic tumor death. The option of combining XPO1 inhibitors with apoptotic inhibitors is one of the options attempted in clinical trials to induce complete/partial remissions in six of 14 patients with refractory acute myeloid leukemia who had received a median of three prior therapies. The options with MDM2, either with BCL-2 or XPO1 inhibitors, could be a strong combination treatment to bring better remission rates, as seen by Nguyen et al. in regards to multiple myeloma. Additionally, the incidence of remission rose among patients who received this combination therapy when compared to azacitidine alone. Hence, based on a thorough understanding of genomic heterogeneity, the use of different permutations in combination with specific inhibitors could be promising in order to address the complexity of this disease. Another advantage of developing combinatorial therapy is to act against the different mutations or against leukemic clone variations seen within the same patient.[30]

CONCLUSIONS

AML is a disease of a highly complex nature with a varied genomic landscape with a number of different mutations, and this complexity has presented a challenge to drug development for nearly five decades. However, the recent development of targeted therapies seeks to resolve this complexity. The main role of targeted therapy is to target the specific abnormality with maximum efficacy. The improved overall survival (OS) rate seen in patients with some of these agents is evidence of positive results that can grant hope to patients, scientists, and physicians. Despite the fact that not all targeted agents were discussed within the contents of this review, we have covered numerous promising agents of interest.

Future Research Directions

Overall, these targeted therapies show promising potential for AML patients. The broader and deeper molecular understanding of this disease has paved the way to address the core problems of treatment. However, there are challenges in regards to designing a proper scientific and clinical trial approach to attain the most accurate efficacy of these targeted drugs to deliver fuller benefits to patients. The phenotype of AML disease has been developed as a consequence of complex genetic and biological pathway changes, hence, addressing its complex nature would not be possible with one specific target, whereas a combinatorial approach could potentially include the various facets of this disease. The continuous and determined focus on understanding the underpinnings of molecular genetics and epigenetics, as well as the persistent surveillance of clonal evolution before and after the treatment of these targeted therapies, could potentially introduce novel changes to the treatment strategies, offering the maximum beneficial outcomes to patients of all ages.

REFERENCES

1. Schönherz, A.A.; Bødker, J.S.; Schmitz, A.; Brøndum, R.F.; Jakobsen, L.H.; Roug, A.S.; Severinsen, M.T.; El-Galaly, T.C.; Jensen, P.; Johnsen, H.E.; et al. Normal myeloid progenitor cell subset-associated gene signatures for acute myeloid leukaemia subtyping with prognostic impact. PLoS ONE, 2020; 15: e0229593.
2. Ediriwickrema, A.; Gentles, A.J.; Majeti, R. Single cell genomics in AML: Extending the frontiers of AML research. Blood, 2022; 141: 345–355.
3. McGrattan, P.; Humphreys, M.; Hull, D.; McMullin, M.F. Transformation of cytogenetically normal chronic myelomonocytic leukaemia to an acute myeloid leukaemia and the emergence of a novel +13, +15 double trisomy resulting in an adverse outcome. Ulster Med. J., 2007; 76; 131–135.
4. Lazarus, H.M.; Vogler, W.R.; Burns, C.P.; Winton, E.F. High-dose cytosine arabinoside and daunorubicin as primary therapy in elderly patients with acute myelogenous leukemia. A phase I-II study of the Southeastern Cancer Study Group. Cancer, 1989; 63: 1055–1059.
5. Boggs, D.R.; Wintrobe, M.M.; Cartwright, G.E. The acute leukemias. Analysis of 322 cases and review of the literature. Med. Baltim, 1962; 41; 163–225.
6. Thomas, D.; Majeti, R. Biology and relevance of human acute myeloid leukemia stem cells. Blood, 2017; 129, 1577–1585.
7. Döhner, H.; Wei, A.H.; Appelbaum, F.R.; Craddock, C.; DiNardo, C.D.; Dombret, H.; Ebert, B.L.; Fenaux, P.; Godley, L.A.; Hasserjian, R.P.; et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood, 2022; 140: 1345–1377.
8. Surveillance Research Program, National Cancer Institute. Available online: https://seer.cancer.gov/statistics-network/explorer/ (accessed on, 27 January 2023.
9. Hirsch, P.; Tang, R.; Abermil, N.; Flandrin, P.; Moatti, H.; Favale, F.; Suner, L.; Lorre, F.; Marzac, C.; Fava, F.; et al. Precision and prognostic value of clone-specific minimal residual disease in acute myeloid leukemia. Haematologica, 2017; 102; 1227–1237.
10. Ley, T.J.; Miller, C.; Ding, L.; Raphael, B.J.; Mungall, A.J.; Robertson, A.; Hoadley, K.; Triche, T.J., Jr.; Laird, P.W.; Baty, J.D.; et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N. Engl. J. Med, 2013; 368: 2059–2074.
11. Kellaway, S.; Chin, P.S.; Barneh, F.; Bonifer, C.; Heidenreich, O. t(8;21) Acute Myeloid Leukemia as a Paradigm for the Understanding of Leukemogenesis at the Level of Gene Regulation and Chromatin Programming. Cells, 2020; 9: 2681.
12. Hanekamp, D.; Cloos, J.; Schuurhuis, G.J. Leukemic stem cells: Identification and clinical application. Int. J. Hematol, 2017; 105: 549–557.

13. Kantarjian, H.M.; Kadia, T.M.; DiNardo, C.D.; Welch, M.A.; Ravandi, F. Acute myeloid leukemia: Treatment and research outlook for 2021 and the MD Anderson approach. Cancer, 2021; 127: 1186–1207.
14. Papuc, S.M.; Erbescu, A.; Cisleanu, D.; Ozunu, D.; Enache, C.; Dumitru, I.; Lupoaia Andrus, E.; Gaman, M.; Popov, V.M.; Dobre, M.; et al. Delineation of Molecular Lesions in Acute Myeloid Leukemia Patients at Diagnosis: Integrated Next Generation Sequencing and Cytogenomic Studies. Genes, 2021; 12: 846.
15. Daver, N.; Venugopal, S.; Ravandi, F. FLT3 mutated acute myeloid leukemia: 2021 treatment algorithm. Blood Cancer J., 2021; 11: 104.
16. Jain S, Kirar M, Bindeliya M, Sen L, Soni M, Shan M, Purohit A, Jain PK. Novel drug delivery systems: an overview. Asian Journal of Dental and Health Sciences, 2022 Mar 15; 2(1): 33-9.
17. Jain S, Purohit A, Nema P, Vishwakarma H, Jain PK. A brief review on nutraceuticals and its application. Asian Journal of Dental and Health Sciences, 2022 Mar 15; 2(1): 7-13.
18. Stasik, S.; Eckardt, J.N.; Kramer, M.; Röllig, C.; Krämer, A.; Scholl, S.; Hochhaus, A.; Crysandt, M.; Brümmendorf, T.H.; Naumann, R.; et al. Impact of PTPN11 mutations on clinical outcome analyzed in 1529 patients with acute myeloid leukemia. Blood Adv., 2021; 5: 3279–3289.
19. Thol, F.; Kade, S.; Schlarmann, C.; Löffeld, P.; Morgan, M.; Krauter, J.; Wlodarski, M.W.; Kölking, B.; Wichmann, M.; Görlich, K.; et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. Blood, 2012; 119: 3578–3584.
20. Song, G.Y.; Kim, T.; Ahn, S.Y.; Jung, S.H.; Kim, M.; Yang, D.H.; Lee, J.J.; Choi, S.H.; Kim, M.Y.; Jung, C.W.; et al. Allogeneic hematopoietic cell transplantation can overcome the adverse prognosis indicated by secondary-type mutations in de novo acute myeloid leukemia. Bone Marrow Transpl, 2022; 57: 1810–1819.
21. Mitrea, D.M.; Grace, C.R.; Buljan, M.; Yun, M.K.; Pytel, N.J.; Satumba, J.; Nourse, A.; Park, C.G.; Madan Babu, M.; White, S.W.; et al. Structural polymorphism in the N-terminal oligomerization domain of NPM1. Proc. Natl. Acad. Sci. USA, 2014; 111: 4466–4471.
22. McClure, R.F.; Ewalt, M.D.; Crow, J.; Temple-Smolkin, R.L.; Pullambhatla, M.; Sargent, R.; Kim, A.S. Clinical Significance of DNA Variants in Chronic Myeloid Neoplasms: A Report of the Association for Molecular Pathology. J. Mol. Diagn, 2018; 20: 717–737.
23. Granowicz, E.M.; Jonas, B.A. Targeting TP53-Mutated Acute Myeloid Leukemia: Research and Clinical Developments. OncoTargets Ther, 2022; 15: 423–436.
24. DiNardo, C.D.; Cortes, J.E. Mutations in AML: Prognostic and therapeutic implications. Hematol. Am. Soc. Hematol. Educ. Program, 2016; 348–355.
25. Purohit A, Jain S, Nema P, Vishwakarma H, Jain PK. Intelligent or smart polymers: advance in novel drug delivery. Journal of Drug Delivery and Therapeutics, 2022 Sep 15; 12(5): 208-16.
26. Borlenghi, E.; Cattaneo, C.; Cerqui, E.; Archetti, S.; Bertoli, D.; Bellotti, D.; Gramegna, D.; Soverini, G.; Oberti, M.; Schieppati, F.; et al. Postremission therapy with repeated courses of high-dose cytarabine, idarubicin, and limited autologous stem cell support achieves a very good long-term outcome in European leukemia net favorable and intermediate-risk acute myeloid leukemia. Hematol. Oncol, 2020; 38: 754–762.
27. Jain S, Purohit A, Nema P, Vishwakarma H, Qureshi A, kumar Jain P. Pathways of Targeted Therapy for Colorectal Cancer. Journal of Drug Delivery and Therapeutics, 2022 Sep 14; 12(5): 217-21.
28. Backhaus, D.; Brauer, D.; Pointner, R.; Bischof, L.; Vucinic, V.; Franke, G.N.; Niederwieser, D.; Platzbecker, U.; Jentzsch, M.; Schwind, S. A high hematopoietic cell transplantation comorbidity Index (HCT-CI) does not impair outcomes after non-myeloablative allogeneic stem cell transplantation in acute myeloid leukemia patients 60 years or older. Bone Marrow Transpl, 2022; 58: 30–38.
29. Network, N.C.C. NCCN clinical practice guidelines in oncology: Adult cancer pain. Available online: https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf accessed on, 18 February 2023.
30. Hilberink, J.; Hazenberg, C.; van den Berg, E.; Mulder, A.; Schuringa, J.J.; van der Helm, L.; de Groot, M.; Choi, G.; de Bock, G.H.; Vellenga, E.; et al. Not type of induction therapy but consolidation with allogeneic hematopoietic cell transplantation determines outcome in older AML patients: A single center experience of 355 consecutive patients. Leuk. Res, 2019; 80: 33–39.