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Acute Myeloid Leukemia in Modern Era: Diagnostic Challenges and Clinical Management

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Abstract

Acute myeloid leukemia (AML) is an abundant type of white blood cells cancer mostly occurs in in adults culminating in deaths. Numerous treatment regimens are available in spite of that many challenges still persist especially in developing countries because they have limited access to early diagnosis, advanced treatments, and supportive care. The aim of this review is to explore the current challenges in diagnosing and management of AML, and to discuss about recent innovations in treatment and diagnostic approaches along with their feasibility. We reviewed published research articles, and review articles from various databases such as Google scholar, Medline, Pubmed, Web of science. Then we extracted relevant information. Major progress has been made in AML treatment, particularly with the introduction of targeted therapies and lower-intensity regimens. For older or unfit patients in whom intensive therapy does not provide favorable outcomes, a combinatory therapy like venetoclax with hypomethylating agents is effective. New drugs such as FLT3 inhibitors, IDH1/2 inhibitors, CPX-351, and gemtuzumab ozogamicin are now part of personalized treatment strategies based on genetic features of the disease. However, access to these therapies and diagnostic tools is still limited in many regions especially developing countries. In spite of innovative treatment regimens death rate after diagnosis remains high in some countries due to late diagnosis, lack of molecular testing, and insufficient supportive care. Although many new treatment regimens are being investigated to treat AML, many patients in still face major barriers to receive immediate and early diagnosis and supportive care. There is a need to expand and equipped healthcare improve access to new therapies, strategies should be made for patient evaluation and treatment planning.

Introduction

Acute myeloid leukemia (AML) is a type of blood cancer which is very rare(1)results mainly (approximately 97.3%) due to somatic mutations(2) it occurs in all ages but mainly in elderly with a median age of 69 years in the white US population (3)while in Algeria and Brazil, mostly AML occurs under the age of 60 years(4).In 2019, approximately 21,450 new cases of AML were diagnosed in U.S. that was 1.2% of all new cases. Incidence of disease was high in aged i.e.25.1% in patients with age 65-74y and was about 33.7% in patients with age 75 or more. Mortality rate increases with age with maximum death rate (43.7%) occurs at 75 y or more (5). Incidence of AML in BritishColumbia was 4.11 per 100,000 population per year(6). Organ mainly affected are gums, lymph nodes and skin. In rare cases, AML can present as an isolated solid tumor (myeloid sarcoma) (7). According to a study, in Saudi Arabia, rate of leukemia ishigh in Females (25%) than male 17%). (8) highest rate was seen in the Eastern Region (9).AML is considered a disease of the elderly population. In the United States, the median age at diagnosis of AML ranged from 62 to 68 years (10).FDA have approved 11 agents for

treatment of AML including Venetoclax, tyrosine kinase 3 (FLT3) inhibitors,15 CPX-351,Isocitrate dehydrogenase 1 and 2 inhibitors, GO (CD33 antibody-drug conjugate),14 oral azacitidine, Glasdageb (hedgehog inhibitor),16 Oral decitabine- cedazuridine. This oral therapy can minimize hospital visits and costs and improve quality of life as well (11). Standard intensive therapy reduces early death rates and enhances survival compared to supportive care which only relieves symptoms and should be given upto 80 years of age(12).Despite advancements, acute myeloid leukemia (AML**)** remains a highly fatal disease, particularly in patients over 60–70 years of age and those unfit for intensive chemotherapy or HSCT (13). However, survival gains were more prominent among women and declined with advancing age (14).The most notable improvements occurred in patients aged 50–75 years, whereas patients aged ≥75 years saw minimal or no survival benefit over time(15). Acute myeloid keukemia (AML) is classified in various categories according to WHO criteria, which is shown in table 1:

Table 1: WHO Classification of AML

AML with defining genetic abnormalities
AML with *RUNX1*:*RUNX1T1*
AML with *CBFB:MYH11* fusion
AML with *DEK:NUP214* fusion
AML with *RBM15:MRTFA* fusion
AML with *BCR:ABL1* fusion
AML with *KMT2A* rearrangement
AML with *MECOM* rearrangements
AML with *NUP 19* rearrangements
AML with *NPM1* mutation
AML with *CEBPA* mutation
AML myelodysplasia related
AML defined by differentiation
AML with minimal differentiation
AML with maturation
Acute basophilic leukemia
Acute monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia
Myeloid sarcoma

Traditional intensive chemotherapy approaches

Conventional chemotherapy regimens are not much effective as reported from a trial as the complete remission with incomplete count recovery was 48% and overall survival was 7.6 months and event free survival was about 2,3 months. Only those patients achieved complete survival who completed multiple cycles of chemotherapy or underwent allogenic stem cell transplant (16).

CPX-351, a liposomal formulation of cytarabine and daunorubicin, is recommended to treat AML.It is used before starting therapy and in those patients with AML-MRC (AML-myelodysplasia related changes). It shows better outcomes, with higher CR/CRi rates (47% vs. 33%) and prolonged overall survival (9.6 vs. 5.9 months) [17]. Although CPX-351 offers meaningful survival benefits, intensive chemotherapy regimens still carry significant risks, often stopping patients with secondary AML from further treatments like transplant or additional

chemotherapy. Oral azacitidine (CC-486) is approved as a long term treatment in patients who cannot take intensive chemotherapy [18].

Inhibitors of AML

Low-dosecytarabine (Ara-C)(20 mg daily)is more effective than palliative care and hydroxyurea in terms of providing complete remission and as a comparator with new treatments. In addition, all trans retinoic acid treatments (ATRA)can make blasts cells sensitive to Ara-C by reducing half -life of BCL-2 which in turns causes increased apoptotic stress (19). Additional inhibitors include men in inhibitors such as Revumenib (effective in relapsed AML with KMT2A translocation)and CD-133 targeted drug-antibody conjugates (20,21). Mutations in genes such as FLT3, NPM1, TP53, KIT, CEBPA, DNMT3A, and IDH are important for prognosis and deciding effective treatments (22). Complex mutations having a mutated P53 mutational gene have more negative impact than individual gene mutations. The clinical impact of a mutation depends upon various factors such as co-mutations, AML subtypes, clone size and treatment strategy (intensive or less intensive(23,24, 25).A lot of researches have been done to understand how AML develops by studying genetic changes that can find hidden anomalies that may be missed out in microscopy. These gene changes help clinicians to decide best treatment for AML.

New Therapies

New therapies that target specific markers in AML have been introduced that include IDH inhibitors (ivosidenib, enasidenib), venetoclax-based therapy, FLT3 inhibitors (midostaurin, gilteritinib, and quizartinib), gemtuzumab ozogamicin, magrolimab and menin inhibitors (keyser). IDH inhibitors are the best choice in patients who are unable to bear chemotherapy or when other treatments do not work (DiNardo et al., 2018; Stein et al., 2017) and these inhibitors also enhance life of patients from 9-12 months (Roboz et al., 2019; Pollyea et al., 2019). In addition,the combination of Venetocla (VEN) which particularly inhibits anti-apoptotic protein BCL-2 and azacitidine can also work in these patients (26). Some cancer cells may also develop resistance even against these inhibitors due to mutations in receptor tyrosine kinase pathway (RTK). Molecular mechanisms mediating relapse following ivosidenib monotherapy in IDH1-mutant relapsed or refractory AML. Blood advances, 4(9), 1894-1905.). IDH1 mutations lead to poor prognosis in patients with AML (27). Many treatment options are available. Since 2017, the FDA has approved eight new targeted drugs, and the EMA has approved six(28). These include various medicines such as tyrosine kinase inhibitors, immune therapies, and drugs that help cancer cells die. To treat FLT3 mutations, is especially important because about one out of three AML patients has this mutation(29). Trials have shown that using a combination of ivosidenib & azacitidine can be more therapeutic during early diagnosis(30). Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia (31). In addition BH3 mimetics are also a good option to treat leukemia stem cells (LSC) induced AML. Biomarkers are needed to be developed to group patients and evaluating the effects of various treatments on targeting LSCs at early stages of AML (32). Patients with NPM1-mutated AML have good prognosis than with FLT3-ITD mutations having poor prognosis, especially among patients with high FLT3 ARs and in the absence of NPM1 mutation. Midostaurin and gilteritinib are type I FLT3 inhibitors and restrain both FLT3-ITD and FLT3-TKD mutations. Sorafenib and quizartinib are type II FLT3 inhibitors that target only FLT3-ITD. Most patients with TP53 mutations do not respond to intensive chemotherapy (33,34).Lower intensity combinations are more effective and tolerable in more than two third of AML patients causing improved and prolonged life span (35).

Isocitrate Dehydrogenate

Isocitrate dehydrogenase (IDH) catalyzes the conversion of isocitrate to alpha-ketoglutarate. There are three isoforms of isocitrate such as IDH1,IDH2 and IDH3(36). In about 20% of acute AML casesIDH1 (8% of AML cases)is mutated at R132 (37) and IDH2 (12% of AML cases) is substituted at R172 or R140(38). Mostly IDH mutations have normal or intermediate karyotype

genetics (39). Genetically IDH1 mutations occur mostly alongwithNPM1 mutations and all these affect DNA methylation (40). IDH mutations culminate in enhanced onco-metabolite named as 2-hydroxyglutarate which blocks cellular differentiation by interrupting histone demethylation(41,42). Outcomes of AML with IDH mutations are inconsistent. According to studies, IDH1/IDH2 mutations combined with NPM1 gene mutations have reduced life span and more chances of relapse(43). Type and location of IDH mutations affect the prognosis of AML. Relapsed cases of AML can be treated by IDH inhibitors such as enasidenib and ivosidenib, but these drugs are not always favorable because primary as well as acquired resistance can be developed. Patients with IDH2 mutations, the combination of venetoclax with azacitidine is the best option (44). Enasidenib is a selective mIDH2 inhibitor. It acts by decreasing levels of 2-HG via inhibiting conversion of α-KG to 2-HG. 2HG vigorously inhibits α keto-glutarate dependent dioxygenases such as histone demethylases and methylcytosine dioxygenases leading to epigenetic dysregulation leading to arrest in differentiation (45). Enasidenib dose about 100 mg daily, can improve overall response rate (ORR) as well as survival (almost 23 months after complete remission) (46). Ivosidenib is also selective mIDH1 inhibitor it also causes diminished levels of 2-HG and with enhanced myeloid differentiation(47). With dosage about 500 mg daily, the ORR and CRc level both improved but maximum survival was less than Enasidenib (18months) in patients achieving complete remission.

FLT 3 inhibitors

Almost 30% of AML cases have FLT3-ITD and tyrosine kinase domain mutations (48). These mutations active FLT-3 as well as its downstream signaling pathways (49). These mutations lead to poor prognosis than FLT3 wild type AML**.** FLT3 inhibitors include quizartinib and gilteritinib. While quizartinib is effective against FLT3-ITD mutations, it lack effectiveness against FLT3-TKD and causes persistent cytopenias due to off-target KIT inhibition (50) Gilteritinib, can target both FLT3 mutations effectively, and have better remission rates and minimum toxicity facilitating transplant in relapsed FLT3-mutated AML (49). Remarkably, gilteritinib is better option even in patients who have received midostaurin or sorafenib.as a first line treatment(51). FLT3 (CD135) is in ~30% of AML cases and is consistently expressed on bulk AML cells and leukemic stem cells (LSCs), The FLT3-targeting BiTE AMG 427 is currently in a phase 1 trial for relapsed/refractory (r/r) AML (52). Midostaurin is an oral FLT3 used for recent cases of AML with FLT3mutation and is scheduled from day 8 through day 15 of treatment cyclegiven on days 8–15 of a treatment cycle after chemotherapy resulting in prolonged survival (53). Midostaurin, an oral multikinase FLT3 inhibitor, showed a significant survival benefit those receiving midostaurin with routinely used cancer therapy had improved survival rate (despite similar CR rates compared to placebo. These results led to its approval for newly diagnosed FLT3-mutated AML (54). It causes nausea, vomiting and diarrhea if administered without (55)and tablets should be aerated 15 minutes before usage. It can cause cardiac toxicity in patients with age 61-70 years. CPX-along with cytarabine and daunorubicin is more than chemotherapy beneficial in patients with non-de-novo AML than chemotherapy(56). As per findings of trial on ivosidenib mono therapy done by DiNardo et al., the drug can be used as first-line therapy for patients with age of 77years, cannot tolerate intensive chemotherapy. This therapy was proved better than traditional treatment such as hypomethylating agents in terms of survival rate (12.6 months) (57). Although IDH1/2 inhibitors are well tolerated, but it can also result in differentiation syndrome in 12 to 15% of patients(58). DS is treated through stopping the IDH inhibitor and starting such as dexamethasone 10 mg twice daily (59). Resistance to IDH inhibitors can arise due to primary or secondary mechanisms, including co-occurring RAS pathway mutations as well as acquired mutations in receptor tyrosine kinase genes or those restoring 2-HG levels can make IDH inhibitors resistance. In order to overcome these challenges, combinatory therapy with IDH1/IDH2 inhibitors can be beneficial (60).

Quizartinib

Quizartinib, a selective FLT3-ITD inhibitor, has been used for newly diagnosed FLT3-ITD–mutated AML based on the phase III QuANTUM-First trial, which showed better overall survival when combined with intensive chemotherapy (60) especially in patients under 60years (61). Unlike quizartinib, midostaurin targets both FLT3-ITD and TKD mutations. A direct comparison between these two regimens have not been done yet.Crenolanib, is being studied along with standard chemotherapy in comparison to midostaurin, based on promising early trial results. All patients with FLT3-ITD mutations should be promptly referred to a transplant center for early evaluation and diagnosis(62).

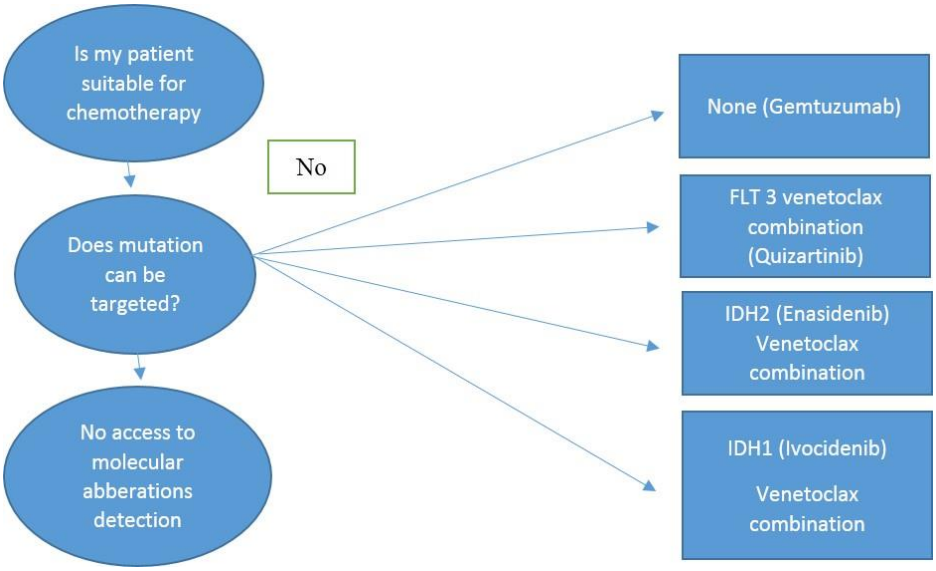

Fig: Simplified treatment plan for AML patients who can't receive intensive chemotherapy

Leukemic stem cells (LSC)-a source of relapse

In AML, survival rate and duration is limited due to remission of AML. This can occur due to DNA altering potential of used chemotherapeutic drugs, existence of resistant cells even after therapy. Analysis of pattern of relapse can lead to better management and monitoring of AML.(63). Studies have shown that LSC graft can give rise to leukemia in immune comprised mice (64).

Pre-LSC are the main causes of relapse in AML(65).

CART T cell therapy in AML

The invention of CART T cell therapy have expanded treatment options for patients with large diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and acute B-lymphoblastic leukemia (B-ALL),multiple lymphoma and Follicular(66). The usage of CART T cell therapy in AML is quite challenging due to expression of many AML associated antigens on normal hematopoietic stem and progenitor cells, causing delayed cytopenias, increased susceptibility to severe infections, and, in some cases, necessitating subsequent donor stem cell transplantation. Additionally, conventional chemotherapy in AML is not beneficial and may causes reduced quantity and function of T cells, which also further reduced the potential of CART T cells. Trials are being done to target AML specific surface markers including CD33, CD123, CLL-1, CD44v6, and NKG2D. The conditioning regimens those used in lymphoma protocols and used in AML patients prior to CART T cell therapy (67). Bisepcific CART T cell strategies like cCAR-T (targeting CLL-1 and CD33) and Biss CAR-T (targeting CD13 and TIM-3) are being investigated in order to improve specificity and reduce toxicity in AML(68,69). Early result have shown its effects on tumour cells mainly and less effects on normal cells(70).

Emerging Therapies Approved for AML

SR NO.	Drug	Drug class	Clinical outcomes in Foundational Trails
1	Oral azacytidine	Hypo-methylating agents	In transplant-ineligible patients ≥55 years achieving CR/CRi within 4 months, 2-year OS was 50.6% vs. 37.1% with placebo [71]
2	CPX--351	Liposomal formulation of daunorubicin and cytarabine	In patients aged 65–75 with high-risk AML, 5-year OS was 18% with CPX-351 vs. 8% with standard chemotherapy [72].
3	Quizartinib	Next-generation FLT3-ITD inhibitor	In 539 patients aged 18–75, combining with 7+3, OS was significantly improved with treatment vs. placebo (median 31.9 vs. 15.1 months) [73]
4	Gemtuzumab ozogamicin	Anti-CD33 monoclonal antibody conjugated to calicheamicin	Enhanced in patients with intermediate or favorable risk [74].

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is a most effective treatment for AML, especially in fit patients with intermediate or high-risk disease, measurable residual disease (MRD), or relapsed/refractory AML [75]. However, access to HSCT is limited in many regions [76]. Recent advancements, such as the introduction of reduced-intensity conditioning (RIC) regimens, have expanded eligibility, allowing older or less fit patients to undergo transplantation. Age alone should no longer be a barrier, particularly as venetoclax-based regimens improve remission rates and hematopoietic recovery [77]. Data from the CIBMTR involving 1,321 patients aged ≥60 years in CR1 demonstrated comparable 3-year overall survival: 49.4% (age 60–64), 42.3% (65–69), and 44.7% (≥70) [78].Historically, myeloablative conditioning (MAC) was preferred for transplant-eligible patients due to better relapse control, despite higher toxicity. However, a phase III BMT CTN 0901 trial challenged this. Among AML/MDS patients randomized to MAC or RIC, MRD status at transplant was key: MRD-positive patients benefited more from MAC (3-year relapse: 67% vs. 19%; OS: 61% vs. 43%), while MRD-negative patients had similar OS regardless of regimen, with lower treatment-related mortality seen with RIC (9% vs. 27%) [79]. This study suggests that RIC is a viable alternative to MAC in MRD-negative patients, offering similar outcomes with less toxicity. This is especially relevant in resource-limited settings, as RIC can be delivered outpatient and without a full HSCT unit [80].

Chemotherapeutic resistance in AML

LSC inherently escape from chemotherapeutic agents via their ability to enter transient states such as quiescence, dormancy, and senescence by mechanism such as resistance to DNA damage(81). Senescence is a complicated phenomenon, resulting from DNA damage, oncogene activation, telomere erosion, protein false folding, high cholesterol diet and oxidative damage(82). Key features of senescence including increased cell size, granularity, and SA-β-gal activity after three days of exposure to Ara-C or anthracyclines, as confirmed from the study (81). Overcoming Venetoclax resistance in AMLVenetoclax is a BCL2 inhibitor, is currently being utilized with hypomethylating agentsor- cytarabine (at low dosage) after FDA and EMA approval (83,84). Overall survival (OS) rate can be enhanced (upto 14.7 months) with azacitidine plus venetoclax and 9.6 months While azacitidone alone, with complete remission DiNardo, (84). Combination of LDAC and venetoclax can improve outcomes in elderly(85). Molecular studies have shown that NPM1 mutations are associated with favorable responses, while TP53

and FLT3-ITD mutations are linked to treatment resistance. The use of HMA plus venetoclax before alloHSCT demonstrated a high ORR of 68.8% in a small cohort, having been approved as remission-induction strategy .Preclinical studies have shown that FLT3 inhibitors combined with venetoclaxcan prevent leukemia via down regulation of anti-apoptotic proteins MCL-1 and BCL-xL with overall response rates (ORRs) ranging from 65–80% for FLT3 inhibitor plus HMA combinatons and up to 85% for FLT3 inhibitor plus venetoclax regimens, both showing acceptable safety profile (86,87).

Next generation immunotherapy targets: CD47 and CD70

CD47

CD47 is a trans membrane glycoprotein found in various tissues such as erythrocytes, platelets, and hematopoietic stem cells. It is expressed by both healthy and malignant cells and was first identified as a tumor-associated antigen in ovarian cancer [88]. It weight is about 50 kDa and is linked to integrins, it was named integrin-associated protein (IAP)(88) . Its level increased in acute myeloid leukemia (AML). CD47 acts as a "don't eat me" signal by binding to SIRPα, an inhibitory receptor on macrophages, dendritic cells, and neutrophils (89). This interaction activates ITIMs and SHP-1/2 phosphatases, disrupting actin–myosin dynamics and inhibiting phagocytosis (90). In the absence of CD47, cells like red blood cells are rapidly cleared by macrophages, highlighting its role in protecting healthy cells from immune clearance (91). The primary ligand of CD47 is SIRPα (also known as CD172a or SHPS-1), an inhibitory receptor expressed on myeloid cells such as monocytes, macrophages, granulocytes, and dendritic cells(89). While other SIRP family members like SIRPβ and SIRPγ can also bind CD47, their functional relevance is unclear (92). CD47–SIRPα binding is relatively weak, species-specific, and influenced by the glycosylation level of SIRPα (93). SIRPα contains three Ig-like extracellular domains, a transmembrane region, and an intracellular tail with two ITIMs, which recruit SHP-1 and SHP-2 phosphatases to inhibit phagocytosis in myeloid cells (90).

CD70

CD70, a ligand of the TNF receptor CD27, mainly expressed on AML blasts and also on leukemic stem cells (LSCs), accountable for survival of these cells, representing a crucial target in AML. The CD70–CD27 interaction causes leukemic cell proliferation while blocking differentiation. Increased levels of soluble CD27 (sCD27) in patient serum are associated unfavorable prognosis(90). The antibody cusatuzumab, which boosts the immune response, was tested with azacitidine in 12 older AML patients. The treatment was safe, and 8 patients had a good response, with 4 showing no signs of disease (MRD-negative). It also reduced leukemia stem cells [91]. New studies are exploring combining cusatuzumab with other drugs and using CD70-targeted CAR-T cells [(92].

Challenges in management of AML

The management of AML is cumbersome and challenging due to numerous reasons such as ineligibility to allo-HCT (especially in elderly), next generation based diagnostic techniques which are rarely available in some regions and are costly, expensive therapies for AML as well as cost of healthcare. Adult patients require prolong and intensive therapy, which is also an economic burden(93). New strategies should be developed to measure economic burden of AML along with establishment of more out-patients clinic for personalized treatment thereby reducing hospital stay (94).

Managing Side Effects of Innovative Drug Combinations in AML

Based on its High toxicity burden and long-term use, HMA/venetoclax (VEN) is a safer regimen. In a study, common grade ≥3 adverse events included named as thrombocytopenia (45%), neutropenia (42%), febrile neutropenia (42%), and infections (64%) (84). Toxicity and myelosuppression can be avoided by treatment delays, shorter VEN duration per cycle, and dose changes(95). Bone marrow evaluation on days 21–28 of cycle 1 helps guide timing for cycle 2

and VEN duration. Patients with ≥5% blasts should continue VEN without interruption. Cycle 2 of HMA/venetoclax should begin on time, even if cytopenias persist. A bone marrow (BM) evaluation is recommended after cycle 2 to assess the patient's response to treatment. Ifno improvement observed after 2 cycles, a change in therapy should be considered, though responses may occurafter 4th cycle. For patients achieving remission after cycle 1 but with ongoing cytopenias, VEN should be stopped and start cycle 2 after 14 days in order to allow for count recovery. In following cycles, VEN duration should be gradually reduced (e.g., 28 → 21 → 14 → 7 days) to limit myelosuppression. If cytopenias last longer than 2–3 weeks, a repeat bone marrow evaluation is needed to check for residual disease. Since HMA/venetoclax therapy may be ongoing, stepwise dose modifications are required for cytopenias that persists. Options include extending cycle length to 5–6 weeks, shortening AZA or decitabine duration, or decreasing their doses (e.g., AZA to 50–25 mg/m², decitabine to 15–10 mg/m² daily). Antimicrobial prophylaxis is recommended from treatment start. Venetoclax is metabolized by CYP3A4 and P-glycoprotein enzymes, when co-administered with strong CYP3A4 inhibitors such as azole anti fungal so its dose should be lowered to 50 mg daily (84,96). The optimal venetoclax (VEN) duration per cycleis not clear. Long-term VIALE-A data showed most duration of about 21 days per 5-week cycle (97). Retrospective studies comparing 2 weeks vs. 4 weeks of VEN with HMAs found similar CR/CRi rates and overall survival, but infections were less with the 14-day regimen, suggesting it as a safer yet effective option (98, 99).

Laboratory diagnosis of AML

AML can be diagnosed by counting myeloblasts in complete blood count, or bone marrow and by observing characteristic sign and symptoms including bruises, bleeding. In some patients AML can cause extra medullary disease affecting CNS (100) and can be detected by positron emission tomography followed by confirmation from biopsy as false positive results can occur due to infections or growth factors. Lumber puncture can also be done in patients having increased white blood cells count(101). According to criteria of WHO at least 20% blasts should be found in bone marrow as well as peripheral smear to declare AML (102) should be included in AML cases, even the blast count is less than 20%. In addition, origin of myeloblasts should be confirmed using myeloperoxidase (MPO) staining, or by increased expression of biomarkers such as CD13,CD33,and CD117 via flow cytometry (103).Risk stratification and treatment option can be determined by using cytogenetic and molecular techniques such as conventional karyotyping (104) which can identify numerical mutations and fluorescence in situ hybridization (FISH) for analysis of recurrent structural chromosomal rearrangements. FISH can also detect cryptic mutations often missed in AML cases with normal karyotyping(105).Measurable residual disease (MRD) is also an important indicator of AML (106).

Conclusion

A lot of improvements have been done for treatment of acute myeloid leukemia (AML). Special tests on leukemia cells are carried out at diagnosis and relapse to better understand the disease, and to decide if a stem cell transplant is needed, and choose the right targeted therapies at earliest ease. For aged patients who are not able to tolerate strong chemotherapy,a combined therapy (venetoclaxwith hypomethylating agents (HMAs)), has helped improve survival. But in some cases, the leukemia becomes resistant to this treatment, often due to specific gene changes like PTPN11 or MAPK pathway activity. Researchers are working to find out who may not respond well and are testing other drugs (like MCL-1 inhibitors) that might work better. In the future, more testing will be required to look closely at leukemia stem cells (LSCs), not just the regular cancer cells, using tools like protein analysis, lab testing outside the body, and immune cell markers. Right now, immunotherapy options in AML are limited, with only gemtuzumab ozogamicin approved. But new treatments are being developed that target leukemia cells more precisely, like those focusing on CD123 and CD47.However, in many poorer countries, patients

still struggle to get these modern tests and treatments. To fix this, doctors, researchers, healthcare workers, and policymakers need to work together, share knowledge, and collect real-world data to improve care for everyone.

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