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Review Article

Clinical Burden and Management of Acute Myeloid Leukemia in the Middle East: Is the System Ready for Precision Medicine?

Marashi M[1*], Awidi A[2], Rustmani AA[3], Alhuraiji A[4], Otaibi AA[5], Mahrezi AA[6], Alshehri B[7], Abdulmajeed B[8], Nasar B[6], El-hemaidi E[9], Soliman H[10], Yaseen HA[11], Motabi I[12], Cheikh JE[13], Alnahedh M[14], Al-Khabori M[15], Alzahrani M[16], Khudair NA[17], Blooshi SA[18], Alwesadi T[19], Al-Shaibani Z[20]

[1]Department of Leukemia, Dubai Authority and Academic Center, Dubai, UAE; [2]Department of Medicine, School of Medicine and Jordan University Hospital, The University of Jordan, Amman, Jordan; [3]Department of Oncology, Burjeel Medical City, Abu Dhabi, UAE; [4]Department of Hematology, Kuwait Cancer Control Center, Kuwait, Kuwait; [5]Department of Oncology, Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [6]Department of Pharmaceutical Services, Sultan Qaboos University Hospital, Muscat, Oman; [7]Department of Pharmaceutical Services, Ministry of National Guard Hospital, Riyadh, Saudi Arabia; [8]Department of Oncology Pharmacy Services, King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia; [9]Department of Hematology, King Abdulaziz Medical City, Jeddah, KSA ; [10]Department of Hematology, Tawam Hospital, AI Ain, UAE; [11]Department of Hematology, Dubai Hospital, Dubai Academic Health Corporation, Dubai, UAE; [12]Department of Adult Hematology and BMT, King Fahad Medical City College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; [13]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; [14]Department of Oncology Pharmacy Services, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [15]Department of Hematology, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman; [16]Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [17]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [18]Department of Medicine, Tawam Hospital, Abu Dhabi health services (SEHA), Abu Dhabi, UAE; [19]Department of Medicine, Prince Mohammed Bin Abdulaziz Hospital, Ministry National Guard - Health Affairs, Almadinah Almunawarah, Saudi Arabia; [20]Department of Medicine, King Fahad Specialist Hospital-Dammam Eastern Province, Dammam, Saudi Arabia

ABSTRACT

Advances in understanding AML's genetic mechanisms have transformed patient management and prognosis. However, implementing precision medicine in the Middle-East faces significant challenges in clinical practice and healthcare systems. Therefore, a panel of 21 experts from the Middle-East held two meetings to highlight AML burden in the region and the current management practice for intensive chemotherapy-ineligible patients. Views on the challenges and accessibility of molecular profiling and targeted therapy were discussed, alongside clinical pharmacists' role in addressing these challenges. They highlighted that the current local data underestimate the disease burden; thus, a national and unified registry for AML cases is recommended. Despite the recent improvement in the referral system for leukemic cases, many challenges still exist, including referral delay, access to tertiary centers, the accessibility to molecular testing and novel agents' availability within the market. The targeted therapies' impact on quality-of-life and indirect treatment costs should be considered critical in the value evaluation of increasing accessibility to novel molecules and diagnostic tools. They also highlighted that clinical pharmacists's role is limited in ensuring the concordance between molecular test results and treatment plans. In the Middle-East, there is a need for clinical pharmacists' involvement in the multidisciplinary decision-making process of AML cases.

Keywords: Acute Myeloid Leukemia (AML); Next-generation sequencing; Targeted therapy; Middle East

INTRODUCTION

Acute Myeloid Leukemia (AML) is a rare hematological malignancy with a notable increasing incidence and related mortality over the past three decades [1]. It is the most common type of acute leukemia in adults, affecting over 16 million people globally in 2019 [1]. Chromosomal translocation, genetic mutations and epigenetic alterations are well-characterized in AML patients and contribute significantly to the pathogenesis of the excessive proliferation and differentiation of myeloid stem cells [2]. AML was long considered an incurable disease with a grave prognosis.

Correspondence to: Mahmoud Marashi, Department of Leukemia, Dubai Authority and Academic Center, Dubai, UAE, E-mail: ahmed.elsawy@servier.com

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However, the progress in our understanding of the genetic and molecular mechanisms of the pathogenesis of AML has resulted in a basic change in the management and prognosis of the patients [3]. It is now well-recognized that AML is a heterogenous disease at molecular levels and that cytogenetic-molecular profiles plays an important role in determining the patient's prognosis and therapeutic options [4–6]. Targeted therapies, such as the Isocitrate De Hydrogenase 1/2 (*IDH1/2*) and B Cell Lymphoma 2 (BCL-2) inhibitors, have demonstrated high antitumor activities and Objective Response Rate (ORR) in AML patients with the targeted mutations [7]. Currently, ivosidenib -an *IDH1* inhibitor- and venetoclax -a BCL-2 inhibitor- are approved by the United States Food and Drug Administration (USFDA) as first-line therapy for elderly AML patients unfit for Intensive Chemotherapy (IC) [8,9]. Despite this basic change in AML management, the prognosis of the patients is still suboptimal, with a reported 5-year Overall Survival (OS) rate ranging from 7.4% to 75% [10–12]. Moreover, elderly patients still show a poor prognosis, with a 1-year OS of less than 30% [13,14]. Such data highlight several unmet needs in the management landscape of AML, including limited availability of molecular testing and some targeted therapies in clinical settings [15].

The burden of AML is growing in the Middle East in terms of the increasing number of patients and its impact on the healthcare system [16–21]. Nonetheless, real-world data regarding the treatment patterns, accessibility to novel molecular profiling techniques and availability of targeted therapies in the region are scarce. Several challenges still face the broad implementation of precision medicine approaches within the clinical practice and healthcare system in the Middle East. The present manuscript summarizes the current burden of AML in the Middle East and the current challenges in improving the accessibility to molecular profiling and targeted therapy in the region for AML patients, whether they are fit for IC or not. This manuscript is based on insights and recommendations that were collected from two expert meetings that gathered the insights of 21 experts from the Middle East. The experts' insights and recommendations were supported by a literature review of the recent advances in molecular profiling and targeted therapies for AML patients to highlight the burden of AML in the region, the current management practice and the challenges in the accessibility of molecular profiling and targeted therapy [22-24].

LITERATURE REVIEW

This article employed a multi-faceted approach to explore the management practices and unmet needs for AML in the Middle East, focusing on the role of targeted therapies. Two expert meetings were held. The first meeting included 14 consultant hematologists from key Middle Eastern countries, including Saudi Arabia, The United Arab Emirates (UAE), Oman, Kuwait, Jordan and Lebanon. During this meeting, participants were engaged through structured open-ended questions formulated to elicit detailed and comprehensive responses. These questions covered three main areas: AML disease burden and workup, practice for molecular testing, the position of targeted therapies in patient management, and the economic value of targeted therapy in the management algorithm of AML. The second meeting engaged seven oncology clinical pharmacists, focusing on their role in treatment decisions, the integration of targeted therapies and the hurdles encountered in molecular profiling and accessibility. To supplement these insights, a detailed literature review was conducted in Medline *via* PubMed. We employed a MeSH-based search strategy to identify recent literature, specifically from the past 15 years, that sheds light on the advancements in molecular profiling and targeted therapies for AML. The MeSH terms central to our search included "Acute Myeloid Leukemia," "Molecular Targeted Therapy," "Genetic Testing," "Epidemiology" and "Middle East." These were utilized individually and in combination to ensure a thorough coverage of the relevant literature. The search was further refined by applying filters for English language and human studies [25].

DISCUSSION

AML burden in the Middle East

As all experts stated, AML data from the Middle East are limited and usually based on single-center registries. According to the global burden of disease statistics, the age-standardized incidence rate of leukemia in the Middle East and North Africa (MENA) was 6.37 per 100,000 populations in 2017, 25 while the incidence of AML was 1.30 new cases per 100,000 populations [26]. This appears to be comparatively lower than the global incidence rate of AML of 1.54 new cases per 100,000 populations [26]. Statistics regarding AML from individual countries are even scarcer (Table 1).

The experts emphasized that the current local data may not represent AML epidemiology in the Middle East and the published figures probably underestimate the disease burden especially in elderly population who are not. Referred to major hospitals and could experience rapid deterioration before referral to specialized centers. Hence, national and unified registries are needed to accurately reflect the region's AML burden and the patient's clinical characteristics [27-29].

Risk stratification and the evolving AML genomic landscape

AML is a complex hematological malignancy that results mainly from genetic mutations in myeloid progenitor cells and exhibits substantial heterogeneity in the pathological pathways, clinical manifestations and therapeutic outcomes [30,31]. The cytogenetic profile aids in diagnosis and predicting treatment response and survival of AML (Table 2) [32]. Therefore, international guidelines recommend risk stratification of AML cases at diagnosis to assess their fitness to receive IC [33-36]. In their 2017 updated classification, the European Leukemia Net (ELN) involved cytogenetics and genomic information to simplify the risk stratification into three prognostic risk groups (favorable, intermediate, or adverse) [6]. More recently, the International Consensus Classification (ICC) introduced three new genetically defined AML categories and qualifiers of the primary diagnosis rather than as specific disease categories (Figure 1) [37]. Moreover, the ELN updated its classification to acknowledge the impact of genetic workouts at initial diagnosis [38]. In the 2022 ELN AML risk classification, the list of genes screening was extended based on the genes defining new entities AML. The updated classification stated that gene mutations *FLT3*, *IDH1*, *IDH2* and *NPM1* should be screened within 3-5 days, along with gene

rearrangements (if available). The rest of gene mutations include CEBPA§, *DDX41, TP53; ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*. Besides, AML mutations with *FLT3-ITD* are now categorized as an intermediate-risk group. In contrast, patients with mutations affecting the bZIP domain of the CEBPA are now considered in the 2022 ELN2 AML favorable prognostic group [38].

In the Middle East, the diagnostic approach to AML has traditionally followed the WHO 2017 classification. Currently, the transition to the latest classifications is still in progress in many Middle Eastern countries. Molecular tests (including actionable mutations, such as *FLT3* and IDH ½) are an integral part of the routine diagnostic workup of AML patients in the Middle East.

Techniques for molecular testing are available in specialized centers across Middle Eastern countries, with geographical variations in the availability of traditional flow cytometry, cytogenetic and molecular testing techniques. Both PCR and Next-Generation Sequencing (NGS) are commonly used for AML patients in the Middle East. Currently, the majority of centers perform *FLT3* and *NPM1* through the PCR technique and the rest of the mutations, including IDH 1/2, are done using the NGS technique at diagnosis. Bone marrow is the specimen of choice for molecular characterization and most tests are done using it. Still, in some special cases, whole blood may be used, mainly in compromised patients unable to go for bone marrow sample withdrawal [39-44].

However, the experts highlighted that several challenges still exist regarding the molecular profiling of AML patients in the region. Some institutions do not have in-house molecular analysis techniques and the samples are sent abroad for analysis [45, 46]. Therefore, many centers can face a delay in the turnaround time for molecular profiling, which could be problematic as the current landscape of AML treatment depends on the molecular profile of the patients. In some centers, the turnaround time may be as long as six weeks (reaching eight weeks if broad panel NGS is requested), resulting in longer turnaround times than the 2022 ELN recommendations. Therefore, there is a need for a centralized laboratory with experienced and skilled personnel covering different Middle East countries. Collaboration between small groups of hospitals and healthcare stakeholders is among the possible solutions for developing qualified central laboratories and faster turnaround time [47]. Other proposed solutions include increasing the availability of in-house PCR, involving the pathologists in the discussion between different stakeholders regarding their needs to shorten the turnaround time and improving the referral system; the referral system can be improved by the establishment of electronic referral system and raising the awareness of the physicians on the appropriate time for referral [48-54].

Table 1: Incidence of leukemia and AML in Middle Eastern countries.

Country	Year	Incidence rate per 100,000 person-years	Ref
Saudi Arabia	2020	Leukemia: 5.6	Globocan
		AML: NR	
UAE	2009	Leukemia: 5.1	Globocan
		AML: NR	
Kuwait	2014-2020	Leukeima: 6.6	Globocan
		AML: 0.55-1.1	Alshemmari et al.
Oman	1996-2015	Leukemia: 5.0	Globocan
		AML Male: 2.5	Al-Lawati et al.
		AML Female: 1.8	
Jordan	2020	Leukemia: 7.4	Globocan
		AML: NR	
Lebanon	2020	Leukemia: 6.8	Globocan
		AML: NR	
Bahrain	2020	Leukemia: 5.1	Globocan
		AML: NR	
Qatar	2020	Leukemia: 5.6	Globocan
		AML: NR	
Egypt	2020	Leukemia: 5.6	Globocan
		AML: NR	

Table 2: Frequency and prognostic values of novel genetic mutations in AML.

Mutation	Prevalence in AML	Prognostic value	Ref
FLT3	ITD in 20%	The ITD-mutated patients showed inferior survival.	[39–42]
	TKD in 5%–10%	Favorable prognosis when *NPM1* co-exists with *FLT3*-TKD	
NPM1	~30%	Patients with *NPM1*-mutated tumors and no high allelic frequency of *FLT3* generally have a favorable prognosis.	[41,43]
DNMT3A	20%	Equivocal results	[44,45]
IDH1 and *IDH2*	*IDH1* in 8%	Equivocal results, but generally associated with inferior survival	[7]
	IDH2 in 12%		
NRAS and *KRAS*	NRAS in 9%	KRAS mutations but not NRAS mutations in AML are directly linked to worse outcomes	[46,47]
	KRAS in 5%		
TET2	6%-27%	TET2 mutation is associated with inferior survival.	[48]
RUNX1	12%	Negative prognostic impact	[49,50]
TP53	5%–15%	Negative prognostic impact	[51]
ASXL1	15%-20%	Negative prognostic impact	[41]
CEBPA	10%–20%	Patients with biCEBPA show favorable prognosis.	[41,52]
	~50% with biCEBPA	Co-occurrence of bZIP with other mutations is associated with poor prognosis.	
KIT	10%-20%	Negative prognostic impact	[53]

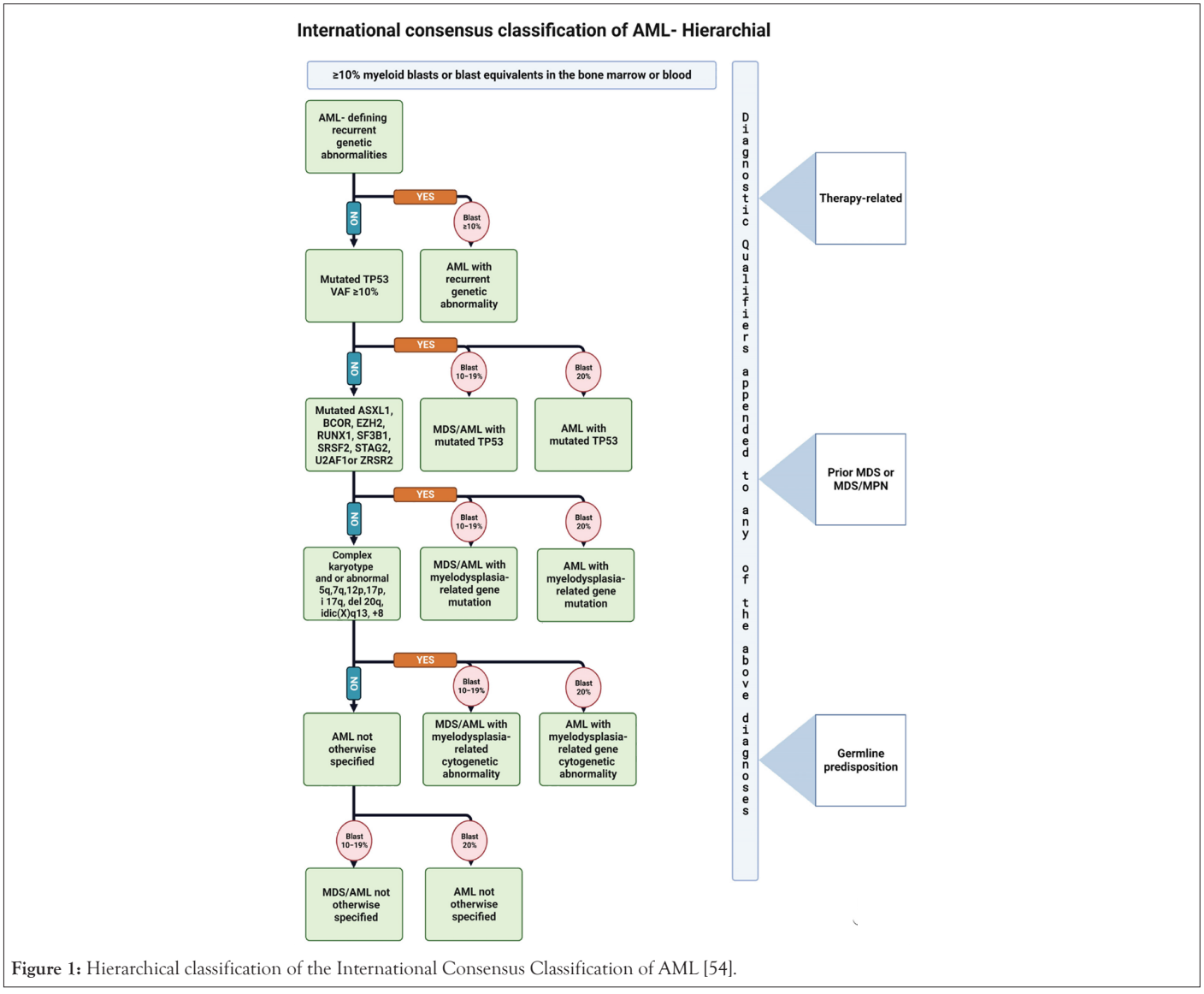

Figure 1: Hierarchical classification of the International Consensus Classification of AML [54].

In addition to cytogenetics and molecular status, Measurable Residual Disease (MRD) is another important prognostic indicator in AML [55]. Previous reports showed that MRD negativity is highly correlated with treatment outcomes. Two methods are currently widely applied (i.e., multiparameter flow cytometry and real-time quantitative Polymerase Chain Reaction [qPCR]) and newer technologies, including digital PCR and NGS [56]. In Middle Eastern countries, MRD assessment is usually requested; however, the current practice regarding MRD timing varies considerably according to the treating center. The lack of wide availability of assessment techniques also limits the facility's ability to perform MRD assessments. The experts highlighted that they decided, in some instances, to perform Allogeneic Stem Cell Transplantation (ASCT) for KIT-mutated Core-Binding Factor AML (CBF-AML) patients without MRD assessment due to the lack of relevant in-house kits and high turnaround time. They also highlighted a need for local guidelines to inform the treating physicians about the time points of MRD assessment.

AML management: The treatment rates of AML have increased over recent years, especially after the introduction of novel agents for IC-ineligible patients [29]. The experts suggested that the treatment rates of AML vary depending on the center's nature. In specialized referral centers, almost 100% of the AML patients are under treatment; however, in regional centers the treatment rate of AML patients may be as low as 70%, which might be due to the higher proportion advanced terminal stage cases who are only eligible for supportive care. Additionally, some patients relapse rapidly and become unfit for available treatment options. Experts further added that patient preference, access to medication and molecular profiling may also contribute to lower treatment rates in some centers. Hence, identifying treatment needs and barriers is of high importance to understand the burden of the disease and to identify potential treatment improvement plans.

The evolving role of targeted therapies in IC-ineligible patients

Newly-diagnosed patients ineligible for IC: Low-intensity treatments with hypomethylating agents were the only treatment options for IC-ineligible elderly patients with AML. However, identifying the molecular impact on vital signaling pathways has induced a new era of AML-targeted therapy with higher efficacy and more favorable outcomes [57]. Novel therapeutics ranged from targeted therapies to monoclonal antibodies [58]. Venetoclax, a selective BCL-2 inhibitor that induces leukemic cell apoptosis, has been extensively investigated in the setting of AML patients unfit for IC. Pivotal phase III trials showed prolonged survival benefits and higher complete remission rates of combining venetoclax with azacitidine or low-dose cytarabine in newly diagnosed patients [59]. Based on these findings, venetoclax combinations are currently approved for newly diagnosed AML patients unfit for IC.

On the other hand, clinical trials have investigated the safety and effectiveness of *IDH1* (e.g., ivosidenib) and *IDH2* (e.g., enasidenib) inhibitors in AML patients, which act as competitive inhibitors of the α-KG-, R132 in *IDH1* and R140Q- and R172K–dependent enzymatic activities in *IDH2*. In early-phase trials, ivosidenib monotherapy demonstrated complete durable remission in 42.4% of the cases, with a median OS of 12.6 months in newly diagnosed AML patients [60]. In May 2019, the FDA approved ivosidenib monotherapy for newly diagnosed AML patients who are ineligible for IC. However, later results from late-phase trials showed that *IDH1/2* inhibitors monotherapy led to a high rate of early relapse [61]. Besides, combination therapy targeting clones or subclones driven by IDH-independent pathways is proposed to improve the response rates and attain durable remission with IDH inhibitors [62]. The phase III trial, AGILE, investigated the efficacy of combined ivosidenib and azacitidine in newly diagnosed unfit patients. Compared to azacitidine monotherapy, the combined arm led to significantly longer OS (median 24 months) and complete remission of 37.5% [63]. The *IDH2* inhibitor, enasidenib, also showed survival benefits in newly-diagnosed patients who are unfit for IC. In a single-arm study, enasidenib led to a response rate of 30.8% and a median OS of 11.3 months [64]. Combined with azacitidine, the combination led to a better overall response than chemotherapy monotherapy (odds ratio 4·9; p=0·0003) [65].

In regards with the Middle Eastern practice, the panel highlighted the lack of universal agreement within their institutions regarding the definition of IC-ineligible patients. However, age cutoff should not be the only criterion to assess eligibility for IC and therapeutic options; the Middle Eastern population shows a high incidence of comorbidities -such as diabetes and cardiovascular diseases, which can render younger patients ineligible for IC. Many centers consider patients older than 65-75 years old with poor performance status and associated comorbidities ineligible. The experts stated that more than one-third of AML patients in the Middle East are IC-ineligible. Although molecular testing is requested for IC-ineligible patients, most experts highlight that they initiate treatment before molecular profiling results due to the long turnaround time. In many centers in the Middle East, venetoclax plus azacitidine or decitabine has become the standard of care for newly diagnosed AML patients who are unfit for IC. In contrast, some centers prefer low-dose cytarabine monotherapy or low-dose cytarabine plus venetoclax.

As per the experts input, effectiveness, tolerability/safety and availability are the most important drivers for treatment selection in the Middle East. For example, despite the promising results of *IDH1/2* inhibitors for IC-ineligible patients with positive IDH mutations, oncologists from the Middle East tend to universally use venetoclax plus azacitidine as frontline therapy due to its availability and lack of information regarding the presence of an actionable mutation at the start of frontline therapy. This shortage represents a major challenge for AML management, necessitating cooperation between the governmental and pharmaceutical industries. Besides, there are several challenges with the venetoclax plus azacitidine combination, including drug interactions, patient compliance, side effects, including infection and febrile neutropenia and high relapse rate. Notably, the majority of experts stated that they would change treatment options after initiating frontline therapy once the results of the actionable mutation test are available. Therefore, it is important to improve the accessibility and turnaround time of molecular analysis, which can guide the initiation of effective targeted therapy in IC-ineligible patients.

Relapsed/refractory patients ineligible to IC: In medically fit R/R patients, IC can be administrated in order to achieve

a second CR before allogeneic HSCT. However, this "bridge to transplant" strategy is unfeasible in most R/R cases. At the same time, low-intensity therapy can be considered palliative care for R/R cases. However, many clinical trials investigated novel agents in R/R patients and demonstrated promising results [66,67]. Both ivosidenib and enasidenib have shown promising results in phase I trials, with an ORR of 40.3%-41.6% in R/R AML patients, leading to FDA approval of both oral molecules in the R/R setting [62]. On the other hand, the second-generation *FLT3* inhibitors, including quizartinib and gilteritinib, demonstrated a significant improvement in remission rate and survival among R/R patients with *FLT3* mutations [68]. Despite this improvement, quizartinib was not approved by the FDA due to concerns over treatment and the robustness of survival benefits. In contrast, gilteritinib was approved by the FDA in 2018 for patients with R/R *FLT3*-mutated AML [69]. The experts highlighted that the outcomes of R/R AML patients in nearly 50% of the cases in the Middle East, remain poor due to acquired resistance mediated by the acquisition or enrichment of signaling genes. In the experts' practice, nearly 50%-70% of the R/R patients are still fit for therapeutic regimens based on their performance status and most of them undergo molecular testing before treatment. Given the current clinical data, the experts stated that *FLT3* inhibitors, ivosidenib and enasidenib would be viable options for R/R patients based on the availability and detected mutations.

Targeted therapies in IC-fit patients

In fit patients younger than 60 years old, cytarabine plus an anthracycline (7+3) is the regimen of choice in favor of risk groups, which achieved a complete remission rate of 70%-80% [70]. When combined with IC, Gemtuzumab Ozogamicin (GO) demonstrated higher survival rates than standard induction therapy alone in patients with CD33-positive [71]. In elderly fit patients, the addition of GO in CD33-positive patients is controversial; recent meta-analysis studies showed that the GO improved Relapse-Free Survival (RFS) but not the OS [72,73]. Notably, the role of *IDH1* inhibitors in newly diagnosed AML patients who are fit for IC is gaining momentum. In a phase I trial assessing the safety and efficacy of ivosidenib or enasidenib combined with IC, the complete remission rates were notably high for both oral molecules (55% and 47%, respectively), with 80% and 63% of the cases became MRD-negative, respectively [63]. Besides, venetoclax combination with IC has been studied in newly diagnosed and R/R fit AML patients and demonstrated a high rate of complete remission, response rate and survival benefits [74].

With regard to patients with FLT-3 mutations, phase III trials showed that midostaurin, a kinase inhibitor of several receptors, including FLT3 protein, significantly improved the OS (median 74.4 months) in new-diagnosed AML patients with *FLT3* mutations [75]. Leading to its FDA approval in 2017 [30]. In *FLT3*-mutated AML cases, midostaurin showed a dramatic improvement in OS when added to standard induction and consolidation regimens [75]. Sorafenib, a multikinase inhibitor, improves survival in patients with newly diagnosed *FLT3*- ITD mutation-positive AML [76]. CPX-351, a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio, represents a significant advancement in the treatment of high-risk AML subtypes. As a dual-drug liposomal encapsulation of cytarabine and daunorubicin, CPX-351 delivers these chemotherapeutic agents in a synergistic 5:1 molar ratio, enhancing their efficacy [77]. It has gained approval from the FDA for treating therapy-related AML (t-AML) and AML with Myelodysplasia-Related Changes (MRC-AML). Clinical studies have demonstrated that CPX-351 leads to a superior ORR and OS when compared with the classical 7+3 regimen (cytarabine and daunorubicin) IC. Notably, while the safety profile of CPX-351 is largely comparable to the 7+3 regimen, it is associated with prolonged myelosuppression [78,79].

Financial consideration and the economic value of targeted therapy in the management algorithm of AML

Direct and indirect treatment costs are another challenge in managing AML cases. Adult patients with AML usually require hospitalization and Intensive Care Unit (ICU) admission due to the disease, comorbidities, or the intensity of therapies. In return, AML patients may represent an additional burden in the ICU setting, especially with the need for close monitoring and prolonged hospital stay [80]. The current basic change in the management of AML opens new horizons, both in terms of clinical and economic values. Compelling evidence suggests that novel drugs reduce the rate of hospitalization and, potentially, its associated cost [81]. Newer options that do not require supportive measures for myelosuppression can also minimize the outpatient cost of routine monitoring of treatment adverse events [82]. Besides, the impact of targeted therapies on Health-Related Quality of Life (HRQoL) and indirect treatment costs should be considered critical in the value evaluation of increasing accessibility to novel molecules and diagnostic tools. In the AML setting, emerging evidence suggests that HRQoL is substantially impaired in IC-ineligible patients and it is significantly correlated with OS; both performance status and treatment response were significant predictors of HRQoL [83]. A previous systematic review found that 70% of the AML treatment cost is attributed to inpatient hospitalization and disease progression, highlighting the role of more tolerable and effective therapies in reducing the overall cost of the disease [84]. Therefore, effective treatment is important to improve the HRQoL of AML patients. Recent reports suggested that novel targeted therapies can have a less negative impact on the HRQoL of the patients compared to standard regimens [83]. In the AGILE trial, combined ivosidenib and azacitidine led to better HRQoL than azacitidine monotherapy [63]. Which can be attributed to a higher response rate, functional improvement and lower incidence of grade ≥ 3 adverse events. However, payers now face the substantial cost of novel agents and their associated genetic analysis, adding significant costs to AML treatment bills, known as financial toxicity. The prices for a single tablet of several AML drugs like gilteritinib, ivosidenib, enasidenib, glasdegib, midostaurin and venetoclax, range substantially, making a month's supply cost anywhere from $7,000 to $28,000. This financial burden can have extreme implications on patients, affecting adherence to treatment and overall well-being [85]. Thus, whether oral targeted molecules provide economic value in the AML population remains questionable. Overall, targeted therapy-such as ivosidenib- can meaningly reduce the economic burden of the AML by decreasing the healthcare resources utilization, healthcare-related costs and hospitalization and improving

the HRQoL of the patients, alongside its clinical benefit [84]. However, the substantial financial burden for patients and payers necessitates a careful consideration of the benefits *versus* costs. Strategies must be developed to reduce the financial burden on patients/payers while still providing them with the best possible care. In the Middle East, several factors govern the choice of AML treatment options in the local practice. In our experience, the cost is an essential driver of treatment choice in AML patients. A considerable proportion of the patients are treated out-of-pocket or have poor insurance coverage. The limitation of treatment reimbursement is a major reason for treatment with less effective treatment for some AML patients in the Middle East and the value-based care model is not adequately applied in many centers. Therefore, efforts are needed to ensure the proper application of the value-based care model and the role of cost-benefit assessment in guiding treatment choices in the region. Besides, effective novel therapies, despite being deemed expensive, may reduce the indirect treatment costs and, hence, the overall cost of treatment compared to the current treatment options. The survival and HRQoL gains from novel therapies may also favor the cost-benefit assessment of these therapies, as the treatment cost would translate into clinically meaningful measurable outcomes. However, it is still early to conclude that novel therapies reduce the overall treatment cost and compelling evidence is still required to assess the cost-benefit of novel therapies.

Role of clinical pharmacists

Clinical pharmacists play an important role in the evolving landscape of AML care. The pharmacist's role involves identifying possible drug interaction, concordance between the treatment plan and molecular profiling, administrating appropriate anti-infective prophylaxis, initiating targeted therapies and managing related toxicities and improving patient outcomes [86]. Experts from the Middle East highlighted that clinical pharmacists have a limited role in managing AML and that pharmacists are usually involved in ensuring the concordance between the treatment plan and molecular profiling; however, they are not involved in the multisectoral discussion about the needed molecular testing or treatment plan. Besides, there is a lack of local guidelines for the role of clinical pharmacists in the management plan. Therefore, there is a need for more involvement of clinical pharmacists in the multidisciplinary decision-making process of AML cases. Clinical pharmacists can also play a role by ensuring that the prescribed treatment runs in line with the results of genetic testing of the patients.

Expert recommendations to improve AML patients' care in middle east countries

To accurately reflect the AML burden and patient clinical characteristics in the region, national and unified registries are essential. Improving accessibility and turnaround time for molecular analysis can be achieved through a centralized laboratory staffed with experienced personnel serving multiple Middle East countries, collaboration among hospitals and healthcare stakeholders to develop qualified central laboratories, increasing the availability of in-house PCR, involving pathologists in stakeholder discussions and establishing an electronic referral system to raise physician awareness on appropriate referral timing. Additionally, there is a need to increase awareness of germline predispositions in myeloid neoplasm patients and establish local guidelines for MRD assessment, with a multidisciplinary team including infectious disease specialists, geriatricians, cardiologists and oncologists. Implementing a value-based care model that considers survival, HRQoL gains and cost-benefit assessments, along with greater involvement of clinical pharmacists in AML decision-making processes, is also necessary.

CONCLUSION

The management of AML in IC-ineligible patients has evolved with the introduction of targeted therapies and novel sequencing techniques. Nonetheless, introducing these novel molecules in routine clinical practice still faces many challenges. In the Middle East, there are limited epidemiological data regarding the overall burden of AML, the percentage of IC-ineligible patients and their characteristics. In return, outreach campaigns, proper diagnostic tools and the availability of novel agents within the market are recommended to overcome the current challenges in the management of AML patients in Middle East countries.

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AUTHORS CONTRIBUTIONS

All authors participated in the meeting and shared their experience and scientific input. All authors were involved equally in the conception and design of the study, analysis and interpretation of the data, the drafting of the paper, and revising it critically for intellectual content. All authors have revised and approved the final version of this manuscript. All authors have revised and approved the final version of this manuscript.

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