Original Article
DOI: https://doi.org/10.70749/ijbr.v3i1.469

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Impact of Infections in Patients with Acute Myeloid Leukemia Receiving Cytarabine+ Daunorubicin (7+3) Versus Azacitidine and Venetoclax during Induction Chemotherapy

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ARTICLE INFO

Keywords

Azacitidine, Venetoclax, Induction, Acute Myeloid Leukemia, Infections, Pakistan, Hematological Malignancy.

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Declaration

Author's Contributions: All authors contributed to the study and approved the final manuscript.
Conflict of Interest: The authors declare no conflict of interest.
Funding: No funding received.

Article History

Received: 03-10-2024
Revised: 16-12-2024
Accepted: 02-01-2025

ABSTRACT

Acute myeloid leukemia (AML) remains a challenging hematologic malignancy, with infections, treatment-related toxicity, and multidrug-resistant (MDR) organisms significantly contributing to high mortality, particularly in resource-limited settings. This study examined infection patterns, MDR prevalence, and induction outcomes in AML patients receiving standard regimens, including Cytarabine-anthracycline (7+3) and azacitidine-venetoclax (Aza/Ven), at a tertiary hospital in Pakistan. In this observational study, 176 AML patients aged ≥18 years treated from January 2018 to December 2023 were analyzed. Patients on the 7+3 (65.3%) and Aza/Ven (34.7%) regimens were assessed for demographics, clinical status, infection rates, organism profiles, antibiotic resistance, and survival outcomes using Kaplan–Meier and Cox regression models. Patients on the 7+3 regimen experienced significantly higher neutropenia and infection rates ($p<0.001$). Among 106 isolates from blood cultures, 12.5% were MDR, with 63% being carbapenem-resistant Enterobacteriaceae (CRE). The Aza/Ven group exhibited a higher induction-related mortality rate (31.1%) compared to 7+3 (21.7%, $p=0.03$). Adjusted analysis revealed a six-fold increased risk of death with the Aza/Ven regimen ($p<0.001$). This study highlights the significant burden of infections and MDR organisms in AML patients, particularly those on Aza/Ven, often reserved for older or high-risk patients. The findings underscore the need for robust infection prevention, stringent antibiotic stewardship, and tailored treatments to optimize outcomes. Further research is essential to refine induction regimens that balance efficacy with infection-related risks, especially in resource-limited settings.

INTRODUCTION

Acute myeloid leukemia (AML) is a myeloid-lineage hematological cancer. Strong induction chemotherapy followed by allogenic stem cell transplantation in a select few patients is the only curative therapy approach due to the lethal character of this aggressive disease [1]. For young, healthy patients, standard induction chemotherapy consists of cytarabine and anthracycline; for elderly, frail patients, or for young patients with several comorbidities and poor performance status at presentation, hypomethylating agents and venetoclax are used.

The management of acute myeloid leukemia is complicated by treatment-related mortality from hemorrhage, infections, and resistant illness. The ideal chemotherapy dosage may be impacted by infections during treatment, which are associated with mortality, morbidity, and higher medical expenses (2). The introduction of a novel combination of azacitidine with venetoclax for the initial treatment of patients' ineligible for intensive chemotherapy has also been explored.

A key obstacle in treating acute myeloid leukemia (AML) continues to be infection. Given the high prevalence of multidrug resistant (MDR) organisms and the significant delay before the initiation of chemotherapy, this issue is of particular concern in developing countries [3]. To develop a suitable plan and

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improve outcomes, comprehending the pattern of infections is crucial. Here, we outline the trends of infections and infection-related mortality among AML patients treated at a tertiary care facility in Pakistan. Compared with conventional chemotherapy, the incidence of infectious complications of venetoclax combined with decitabine or azacitidine significantly decreased. Pretreatment high leukemia burden and fever were independent risk factors for infections.

OBJECTIVES

To evaluate the frequency of infections and infection-related outcomes in patients receiving cytarabine and daunorubicin vs azacitidine and venetoclax during induction chemotherapy.

MATERIALS AND METHODS

In this observational prospective study, data was recorded on prefilled Pro Formas of all acute myeloid leukemias patients older than 18 years of age admitted to Aga Khan University Hospital Karachi from January 2018 until December 2023. Approval was obtained from AKU's ethical review committee (ERC) (ERC #: 2024-9797-28491) before starting the study.

This information included the patients' demographics, the disease initial characteristics and laboratory values, the induction course and any problems, the induction outcome, and the patient's status as being in remission at the end. SPSS 21 was used to enter and analyses the collected data for results and descriptions.

Confidential files and computerized medical data were searched for patient information. Demographic information, presenting symptoms, clinical findings, Eastern Cooperative Oncology Group performance status, comorbidities present, infectious foci at presentation and laboratory parameters. We also documented the type of organism on culture, response to antimicrobials, deterioration of patients on antimicrobials and need for admission in special care and intensive care units. The amount of time between the diagnosis and the beginning of induction was also noted.

Inclusion Criteria

1. All patients above 18 years of age.
2. All patients diagnosed with Acute myeloid leukemia.
3. Relapsed Acute myeloid leukemia.
4. AML refractory to standard induction and salvage chemotherapy.
5. CML transformed in AML.

Exclusion Criteria

1. All leukemias other than acute myeloid leukemia.
2. Acute promyelocytic leukemia.
3. Therapeutics

All patients who were younger than 50 years of age and who did not have any significant comorbidities were treated with standard intensive therapy with 7+3-based induction (cytarabine from 100 mg/m2 from Days 1-7 along with daunorubicin from 60 mg/m2 from Days 1-3) [4], whereas patients older than 50 years of age or those younger than 50 years of age with multiple comorbidities or poor performance status received azacitidine in combination with venetoclax. Azacitidine was administered subcutaneously at a dose of 100 mg once daily for 7 days. Venetoclax was administered in combination with Voriconazole (a strong CYP3A4 inhibitor) during induction at a dose of 100 mg and was continued for 21 days. However, in the context of worsening cytopenia venetoclax was stopped earlier. Bone marrow biopsy to document remission was performed on day 28.

Supportive Care

Either from the Haematology Outpatient Clinic or the emergency room, patients were admitted to the hospital for AML induction. During the induction phase, patients were kept in the hospital until their neutropenia had subsided and there was no longer any indication of an active infection, and they were no longer in need of blood product support.

A peripherally inserted central catheter (PICC) was used to deliver chemotherapy. Until their blood counts improved, individuals undergoing 7+3 induction chemotherapy were kept as inpatients. Before remission was noted on day 28 of the bone marrow biopsy, G-CSF was not given. All patients received voriconazole 200 mg PO BID as antifungal prophylaxis along with routine antibiotic and antiviral prophylaxis with ciprofloxacin 500 mg PO BID and acyclovir 200 mg PO BID respectively. Blood products were transfused as needed. Platelets were transfused in cases of bleeding or when the platelet count decreased to < 10 x 10^9/L (< 20 x 10^9/L in febrile patients). Packed red cell concentrates were transfused when hemoglobin dropped to less than 8 g/dl.

A thorough history and physical examination aimed at identifying the focus of infection, radiologic studies where needed, and cultures were used to assess every episode of fever [5]. Whenever an infection was suspected, cultures were taken from PICC line and peripheral blood in accordance with the institutional one hour sepsis bundle which comprises measuring lactate levels, obtaining blood cultures before antibiotic administration, administering broad-spectrum antibiotics, beginning rapid administration of crystalloid at a rate of 30 ml/kg if hypotensive or lactate > 4 mmol/L and applying vasopressors if hypotensive during and after fluid resuscitation to maintain a mean arterial pressure > 65 mmHg. When clinically necessary, cultures were also obtained from other locations (such as

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sputum, urine and stool). Beta D glucan and galactomannan was also sent from peripheral blood to investigate possible fungal infection. For patients with predominant chest symptoms with no other proven focus of infection who continued to be febrile, bronchoalveolar lavage was also performed. Every episode of infection was graded on the MEWS (modified early warning sign) score, and appropriate action was taken accordingly. Patients were usually escalated to broad-spectrum antibiotics usually meropenem. In cases of suspected or proven venous line infection vancomycin was added. The choice of subsequent change or total duration of antibiotic treatment was consistent with the hospital's Infectious Diseases Team policy. Amphotericin was added empirically if fever continued beyond 72 hours or if beta-D glucan/galactomannan revealed abnormal results.

Microbiological Analysis

Every microbiological test was carried out at the hospital laboratory of Aga Khan University. The College of American Pathologists (CAP) has granted this lab its accreditation. The American Society of Microbiology's recommendations were followed when performing the cultures. Blood cultures were carried out in BioMerieux's BacT/Alert. Biochemical reactions and APIs were used to identify bacteria phenotypically. The Vitek 2 Yeast ID card (bioMerieux, France) was used to identify the yeasts. The Kirby-Bauer disc diffusion method was used to test for susceptibility on Muller-Hinton agar (MHA) and VITEK 2 (BioMerieux). The CLSI M100 most recent edition was used to interpret susceptibilities by year.

Operational Definitions

Induction: Induction therapy is the initial stage of treatment. Remission and illness control are the objectives of induction therapy.

Bone marrow blasts <5%, no extramedullary leukemia, absolute neutrophil count >1.0 × 10^9/L, platelet count >100 x 10^9/L, and no need for red cell or platelet transfusions are all indicators of complete remission. The period of time between randomization and death is known as overall survival, or OS. Patients who were still living at the time of evaluation or lost to follow-up were excluded. The period of time between randomization and the onset of disease progression or death is known as progression free survival, or PFS. Time between randomization and an event, such as the advancement of a disease, the cessation of treatment for whatever reason, or death, is known as event-free survival, or EFS. Organisms that have acquired nonsusceptibility to at least one agent in three or more antimicrobial categories are known as multi-drug-resistant organisms, or MDRs [5]. Death that takes place within 30 days of starting AML treatment is known as "induction mortality." Statistical Analysis: SPSS version 20.0 was used to analyse the data. Fisher's exact test was used to analyse categorical data, and the independent sample t test was employed for continuous data. To evaluate the overall survival (OS) of the patients, Kaplan-Meier survival curves were created. The median survival times were compared using the log-rank test. The reported survival rates were accompanied by the appropriate 95% CIs. The p-values and risks were adjusted for significant covariates using a Cox regression model. In the analysis, a significant level of p-value ≤.05 was applied.

RESULTS

Our study comprised 176 patients who had been diagnosed with acute myeloid leukemia. A descriptive summary of the patient characteristics in both groups is presented in Table 1. Of these patients, 61 (34.7%) received induction therapy with azacitidine and venetoclax (Aza/Ven arm), while 115 (65.3%) received cytarabine and daunorubicin (7+3 arm). Patients in the Aza/Ven arm were 58.5 ± 12.8 years old on average, while those in the 7+3 arm were 37.2 ± 13.0 years old. With a mean age difference of 21.4 [17.3–25.4] years, patients in the 7+3 arm were, on average, younger than those in the Aza/Ven arm. This difference was statistically significant, with a p value less than 0.001. With 115 (65.3%) male patients, Males made up the majority of our group. The 7+3 arm experienced a complete count recovery period of 25.0 ± 9.0 days after introduction, while the Aza/Ven arm experienced a recovery period of 9.0 ± 7.0 days. With a p value smaller than 0.001, this 15.8 [95% CI = 13.1–19.5] day difference was likewise statistically significant. 84 (53.8%) of the 156 (88.6%) individuals who had blood cultures had positive results. With a p value of 0.013, a statistically significant correlation was found between the type of induction regimen and the existence of growth on blood cultures. Only 16 (10.7%) of the 149 (84.7%) patients whose urine cultures were done produced growth of isolates. However, there was no correlation seen between the type of development on urine cultures and induction regimen with a p value of 1.000. Organisms found on blood cultures from patients in the two therapy arms are displayed in Table 2. The most prevalent organisms were Enterobacter spp. (n=14), E. coli (n=16), and Coagulase negative Staphylococcus species (CoNS) (n=32). The resistance patterns in our patient population are displayed in Fig. 1. Of the isolates, 22 multidrug-resistant (MDR) organisms were found to be present, representing 12.5% of the total. The bulk of them, 14 isolates (63% of MDR cases), were carbapenem-resistant Enterobacteriaceae (CRE), followed by 5 isolates (23% of MDR cases) of vancomycin-resistant enterococci (VRE). Both induction arms' survival results are shown by the Kaplan-Meier curves in Figure 2. 25 patients (21.7%) on

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the 7+3 regimen and 19 patients (31.1%) on azacitidine plus venetoclax experienced induction-related death the log-rank test ($p < 0.001$). The multivariable Cox proportional hazard regression's findings are shown in Table 3. Covariates in the model included blood culture results, age, sex, and the type of induction regimen. After controlling for variables, this result shows that the only factor that significantly affected the risk of death in our patient sample was regimen type. Compared to patients who got 7+3, those who received Aza/Ven had a 5.76 95% CI = 2.72–12.20 times higher risk of dying. There was no statistically significant increase in the risk of death linked to the growth of organisms on blood culture ($p = 0.185$).

Table 1

Descriptive summary of patient characteristics among both groups

Variable	Cytarabine + Daunorubicin n (%)	Azacitidine + Venetoclax n (%)	Total n (%)
Gender	70 (60.9)	45 (73.8)	115 (65.3)
Male	45 (39.1)	16 (26.2)	61 (34.7)
Female			
Age	86 (74.8)	9 (14.8)	95 (54.0)
< 50	23 (20.0)	19 (31.1)	42 (23.9)
50 – 60	6 (5.2)	33 (54.1)	39 (22.2)
> 60			**P<0.001**
Count Recovery Post-Induction (days)	25.0 ± 9.0	9.0 ± 7.0	19.5 ± 11.4
Blood Culture	67 (60.4)	17 (37.8)	84 (53.8)
Growth	44 (39.6)	28 (62.2)	72 (46.2)
No Growth			**P = 0.013**
Death	25 (21.7)	19 (31.1)	44 (25.0)
Consolidation	82 (71.3)	33 (54.1)	115 (65.3)
Loss to follow	6 (5.2)	9 (14.8)	15 (8.5)
Palliative care	2 (1.7)	0 (0.0)	**2(1.7)**
			P = 0.03
Percentage resistant* isolates identified on BLCS	20 (29.8)	2 (11.8)	22 (12.5)

Isolate was resistant to at least one antibiotic on sensitivity testing. These include MDR organisms

Figure 1

Resistance patterns in our patient population.

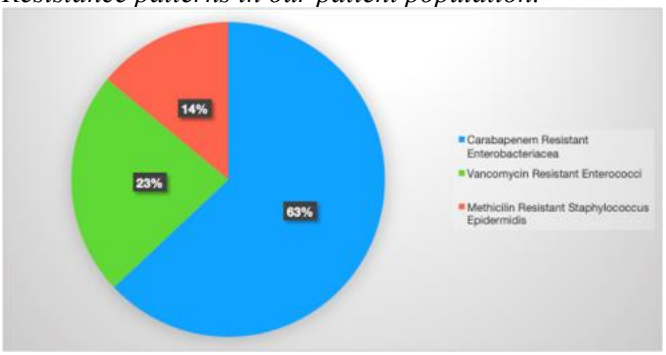

Figure 2

Kaplan–Meier Curve Survival outcomes for both induction arms.

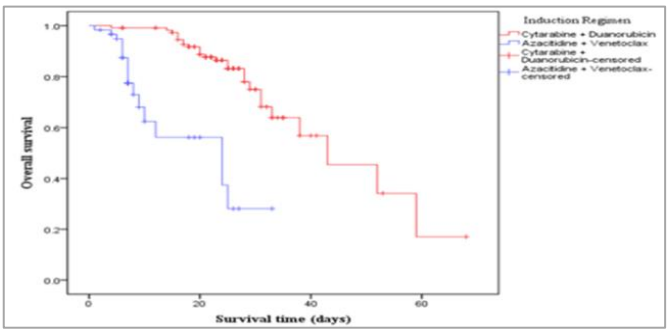

Table 2

Organisms identified on blood cultures from patients among the two treatment arms

Organisms identified on blood culture	Type of Organism	Cytarabine + Daunorubicin n (%)	Azacitidine + Venetoclax n (%)	Total n (%)
Staphylococcus (CN)	Gram-Positive	25 (28.1)	7 (41.2)	32 (30.18)
Enterococcus spp	Gram-Positive	8 (9.0)	-	8 (7.5)
Corynebacterium spp	Gram-Positive	6 (6.7)	1 (5.9)	7 (6.6)
Streptococcus spp	Gram-Positive	2 (2.2)	-	2 (1.88)
Enterobacter spp	Gram-Negative	12 (13.5)	2 (11.8)	14 (13.2)
Escherichia Coli	Gram-Negative	11 (12.4)	5 (29.4)	16 (15.09)
Acinetobacter spp	Gram-Negative	7 (7.9)	-	7 (6.6)
Pseudomonas spp	Gram-Negative	4 (4.5)	1 (5.9)	5 (4.7)
Klebsiella Pneumoniae	Gram-Negative	4 (4.5)	-	4 (3.7)
Proteus Mirabilis	Gram-Negative	-	1 (5.9)	1 (0.9)
Providencia spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Stenotrophomonas spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Bacteroides spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Aeromonas spp	Gram-Negative	1 (1.1)	-	1 (0.9)
Candida spp	Yeast	6 (6.7)	-	6 (5.6)
Total Isolates identified		89 (84.0)	17 (16.0)	106

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*Multiple isolates were identified in some patients; hence the number here does not represent the total number of patients with a given organism but rather the number of individual organisms identified on blood culture. CN – Coagulase Negative.

Table 3
Multivariable Cox hazard model

Variable	Hazard Ratio	95% C.I	p value
Age	1.01	[0.99 – 1.04]	0.299
Gender	2.025	[0.92 – 4.45]	0.079
Male		-	
Female	Reference		
Regimen	5.76	[2.72 – 12.20]	< **0.001**
Azacitidine + Venetoclax		-	
Cytarabine + Daunorubicin	Reference		
Blood Culture	0.63	[0.32 – 1.21]	0.185
No Growth		-	
Growth	Reference		

DISCUSSION

This study offers a thorough examination of infection rates and related consequences in patients with acute myeloid leukemia (AML) after induction chemotherapy using either azacitidine + venetoclax (Aza/Ven) or cytarabine + daunorubicin (7+3). The difficulties in treating AML in a tertiary care setting in Pakistan are reflected in our data, which show a high infection burden during induction chemotherapy 53.8% of the participants in the current study had positive blood cultures. This is greater than comparable studies by the Polish Adult Leukemia Group (PALG), which showed 26% blood culture positive [2], but comparable to research published in the Indian subcontinent, which showed 51% blood culture positivity [6]. On the gram-negative side, 42 organisms were isolated, with Enterobacter species being the predominant pathogen. For patients receiving Aza/Ven, 8 gram-positive and 9 gram-negative organisms were isolated, with CoNS and E. coli being the most frequently identified in each respective category. When both groups were combined, the total number of gram-positive and gram-negative organisms was nearly balanced, with 49 gram-positive and 51 gram-negative organisms. Among the gram-positive organisms identified, coagulase-negative staphylococci (CoNS) were deemed pathogenic in only 16 cases (32.6%) based on specific criteria. These criteria's included fever >100°F, septic appearance, systolic blood pressure <90 mmHg, and the presence of risk factors such as long-term intravascular catheterization or immunosuppression with central lines. These findings are consistent with Khan et al., who reported CoNS as pathogenic in 34.78% of cases [8]. Similarly, Maranda et al. identified CoNS as the most frequently isolated gram-positive pathogen (28%) in a comparable cohort [2]. These results highlight the importance of evaluating the clinical significance of CoNS in infection management for immunosuppressed patients. Our results demonstrated a greater incidence of infections in patients treated with the 7+3 regimen than in those receiving Aza/Ven. This is likely due to the extended duration of neutropenia typically associated with the 7+3 regimen, which results in prolonged exposure to opportunistic pathogens. These findings align with those of previous studies, such as those of Osmani et al. who reported higher infection rates with gram-negative organisms in neutropenic patients undergoing intensive chemotherapy [9]. A recent study by López et al. reported a higher incidence of infections (78% compared to our 53.8%) but a lower 30-day mortality rate (10% vs. 21.7%–31.1%) in patients with Acute Leukemia [10]. This discrepancy in mortality may be attributed to differences in the severity of illness, patient age, Leukemia subtype or resource limitations in our setting. Notably, while both studies identified Gram-negative bacteria as the primary pathogens, our findings showed a more balanced distribution between Gram-positive and Gram-negative organisms. A significant finding of our study is the prevalence of multidrug-resistant (MDR) organisms, with 12.5% of isolates being MDR and carbapenem-resistant Enterobacteriaceae (CRE) accounting for 63% of these. This is slightly lower than the 17.3% incidence reported by Kumar et al. in India, likely reflecting regional differences in antimicrobial stewardship, healthcare infrastructure, and resistance patterns [6]. These findings underscore the importance of tailored infection control measures to address the challenges posed by MDR organisms in diverse healthcare settings. The rise of MDR pathogens severely limits therapeutic options, complicates infection management, and is associated with increased mortality. This underscores the critical need for stringent infection control measures, enhanced antimicrobial stewardship, and judicious use of broad-spectrum antibiotics to prevent the spread of MDR organisms. Survival analysis revealed notable differences between the two induction regimens. Patients receiving the Aza/Ven regimen experienced significantly lower overall survival than those receiving the 7+3 regimen did, with induction-related mortality rates of 31.1% versus 21.7%, respectively. Regional studies of Indian sub-continent, such as those by Rija et al. [11] and Philip et al. [3], reported a higher induction-related mortality of 27.5% and 24.7% respectively in de novo AML patients treated with the 7+3 regimen. In contrast, induction mortality in other Indian institutes and Western centres, has significantly improved, with an induction related mortality of 15.6% reported by Pandian et al. [12], Kumar et al reporting a rate of 15.6% [6], Bahl et al. reporting a rate of 17.1% [13] and Polish Adult Leukemia Group (PALG) reporting an induction related mortality of 9% [2]. These variations underscore disparities in healthcare infrastructure, infection control,

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and supportive care between regions. Our institute monitors induction-related mortality for patients receiving the standard 7+3 treatment, aiming for a benchmark of <17%. Annual mortality rates from 2018 to 2023 were 12%, 28%, 20%, 16%, 12%, and 12%, respectively However, it is important to consider that selection bias may have contributed to the higher mortality rates observed with the Aza/Ven combination, as many patients in this cohort were of advanced age, had multiple comorbidities, or had previously received standard first-line chemotherapy but experienced relapse or refractory disease. Among this cohort 12(63%) patients who experienced induction related mortality were given Aza/Ven as first line therapy, whereas 7(36.8%) patients received Aza/Ven as second- or third-line therapy. Our study emphasizes the importance of early and aggressive management of infections in AML patients, especially those undergoing intensive chemotherapy. The high prevalence of MDR organisms highlights the need for robust antimicrobial stewardship programs and innovative therapeutic approaches to address resistant infections. Furthermore, the poorer survival outcomes associated with the Aza/Ven regimen underscore the necessity of refining patient selection criteria and optimizing treatment protocols for elderly and frail AML patients. While the presence of MDR infections is concerning, our findings suggest that the type of induction regimen is an even stronger predictor of mortality. Future research should focus on validating these results in larger, multicenter cohorts and exploring the potential benefits of incorporating targeted therapies and personalized medicine in AML management. Overall, this study provides valuable insights into infection-related challenges in AML treatment and highlights critical areas for intervention to improve patient outcomes.

CONCLUSION

This report emphasizes how common infections are in AML patients receiving induction chemotherapy, especially in environments with inadequate resources. The results show that whereas patients treated with the Aza/Ven regimen—usually older patients or those with comorbidities—face increased induction-related mortality, those treated with the 7+3 regimen have higher rates of infection as a result of extended neutropenia. The management of infections and patient outcomes are made more difficult by the proliferation of multidrug-resistant pathogens, especially carbapenem-resistant Enterobacteriaceae (CRE). The findings highlight the necessity of strict infection prevention measures, such as improved supportive care, individualized treatment plans, and strong antimicrobial stewardship. Improving survival rates requires adjusting treatment to strike a balance between effectiveness and infection-related hazards. To reduce mortality and improve care for AML patients, more research is required that focusses on induction regimen optimization and region-specific issues especially in developing healthcare systems.

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