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Original Article

Safety and infection risk factors in elderly acute myeloid leukemia patients undergoing induction therapy with venetoclax combined with hypomethylating agents

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Abstract: Objective: To retrospectively analyze the incidence of infections in elderly acute myeloid leukemia (AML) patients undergoing induction therapy with venetoclax combined with hypomethylating agents and to compare these findings with those from patients receiving standard or low-dose chemotherapy. Methods: Medical records of 169 elderly (≥60 years old) AML patients diagnosed via MICM (morphology, immunology, cytogenetics, and molecular genetics) at the First Affiliated Hospital of USTC between June 2019 and June 2022 were reviewed. Patients were divided into three groups: venetoclax combined with hypomethylating agents group (targeted therapy group), standard chemotherapy group, and low-dose chemotherapy group. Comparisons were made across groups regarding bacterial infection rates, fungal infection cases, infection sites, and severity. Results: The median ages at diagnosis in the targeted therapy group, standard chemotherapy group, and low-dose chemotherapy group were 73, 68, and 71 years, respectively ($P<0.05$). Compared with the standard chemotherapy and low-dose chemotherapy groups, the targeted therapy group had a higher prevalence of comorbidities ($P<0.05$). Complete remission rates in targeted therapy group, standard chemotherapy group, and low-dose chemotherapy group were 68.8%, 51.2%, and 26.4%, respectively ($P<0.05$). The durations of neutropenia were 9.0±8.4, 15.0±15.0, and 9.3±9.1 days, respectively ($P<0.05$). Bacterial infection rates were 87.5%, 95.2%, and 94.3% ($P<0.05$), with the most common sites being the lungs, bloodstream, upper respiratory tract, and unspecified sites. The durations of fever were 2.34±3.59, 4.52±4.38, and 3.53±4.76 days, respectively ($P<0.05$). The proportions of patients receiving antifungal prophylaxis were 46.8%, 46.4%, and 41.5%, respectively ($P>0.05$), mainly involving voriconazole and posaconazole. The proportions of clinically diagnosed or confirmed fungal infections were 6.3%, 9.5%, and 9.4%, respectively ($P>0.05$). The proportions of patients requiring initiation of antifungal therapy were 34.4%, 48.8%, and 43.4%, respectively ($P<0.05$). Among the 169 elderly AML patients, three (1.8%) developed infection-induced multiple organ dysfunction syndrome (i-MODSE), all in the standard chemotherapy group. Conclusion: Venetoclax combined with hypomethylating agents shows a favorable safety profile and reduced infection risk in the treatment of AML in the elderly patients. Meanwhile, nontargeted therapies, a prolonged duration of neutropenia, and a prolonged duration of fever were found to be independent risk factors for fungal infections and the need for antifungal intervention.

Keywords: Acute myeloid leukemia, venetoclax, hypomethylating agents, initial induction therapy, infection

Introduction

Acute myeloid leukemia (AML) is one of the most prevalent hematologic malignancies in China, with its incidence rising significantly with age. Approximately 75% of patients are diagnosed between ages of 55 and 65, with a median age of around 68 years [1]. AML treatment often involves extended therapy, which often leads to bone marrow suppression and neutropenia after chemotherapy. Additionally, elderly AML patients frequently present with multiple comorbidities and poor tolerance, resulting in an increased risk and severity of infections.

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Currently, there is no standardized treatment for AML in the elderly. Traditional AML treatment involves induction therapy followed by post-induction consolidation. Over the past 40 years, there has been little progress in induction therapy for AML; the classic induction regimen remains a 3-day course of anthracyclines combined with 7-day course of cytarabine (Ara-c). This standard chemotherapy combination has been shown to reach a complete remission (CR) rate of 50% and a 5-year overall survival (OS) rate of 40% in patients under 60 [2]. However, for patients over 60, the CR rate drops to 30%, with a 5-year OS rate of only 10% to 20%, and an OS rate of 5% or less when adverse cytogenetic factors are present [3, 4]. A study showed that among AML patients over 65 years old, 64% received treatment, yet their median survival time was only 1.7 months [5]. These findings underscore the urgent need for improved treatment strategies to enhance AML outcomes in elderly patients.

In recent years, the rapid development of sequencing technologies has led to the discovery of numerous reproducible epigenetic genes, with DNA methylation and histone modification abnormalities emerging as promising therapeutic targets for hematological malignancies. These discoveries have provided new therapeutic idea for the elderly AML patients who are not able to tolerate intense chemotherapy. Decitabine, a nucleoside analogue, induces hematopoietic cell differentiation and promotes DNA demethylation. With reduced doses of pre-stimulation regimens, decitabine shows fewer adverse effects and high tolerability, making it widely used in AML treatment. The B-cell lymphoma-2 gene (Bcl-2) gene, a key regulator of tumor cell apoptosis, is also a novel target for the clinical treatment of leukemia. Venetoclax (VEN), the first marketed oral inhibitor of BCL-2, triggers rapid apoptosis in AML cells and enhances their sensitivity to demethylating drugs. Since the introduction of VEN in China in December 2020, an increasing number of elderly AML patients have started receiving VEN-based induction therapies, commonly combined with hypomethylating agents (HMAs). However, there are few reports on the efficacy and safety of VEN in combination with hypomethylating agents for AML treatment. Additionally, systematic comparative studies on the response and infection profiles of elderly AML patients treated with VEN-HMA regimens are lacking compared with elderly AML patients treated with standard chemotherapy or low-dose chemotherapy.

In this study, we conducted a comparative analysis on a relatively large number of cases, systematically analyzing the infection profiles and characteristics of elderly AML patients undergoing initial induction therapy with various treatment approaches. We also aimed to identify associated risk factors, providing objective evidence to inform clinical prevention and treatment strategies.

Materials and methods

Study population

This retrospective study reviewed the medical records of 169 AML patients diagnosed via MICM (morphology, immunology, cytogenetics, and molecular genetics) and treated with inpatient chemotherapy at the First Affiliated Hospital of USTC between June 2019 and June 2022. This study was approval by the Ethic Committee of the First Affiliated Hospital of USTC.

Inclusion criteria: (1) Adult AML patients, with the diagnosis based on at least one inpatient or two outpatient records meeting an AML International Classification of Diseases, Ninth Revision/Tenth Revision (ICD-9/ICD-10) diagnosis code [6] (ICD-9 code: 205.0; ICD-10 codes: C92.0, C92.5, C92.6, C92.9, C92.A); (2) Age ≥60 years old; (3) Patients who had continuous care for 12 months and ≥60 days in the follow-up period; (4) A minimum survival period of one month after the completion of chemotherapy; (5) Patients with complete clinical files. Exclusion criteria: (1) Patients diagnosed at our hospital but did not complete a full course of induction chemotherapy or who did not receive chemotherapy for other reasons; (2) Patients whose AML developed from other hematologic malignancies; (3) Patients with other primary cancer, metastatic disease, myelodysplastic syndromes, or myelofibrosis in the baseline period; (4) Patients with incomplete clinical files. The flow chart of the study is shown in **Figure 1**.

Before December 2020, the primary treatment regimens used for AML were standard

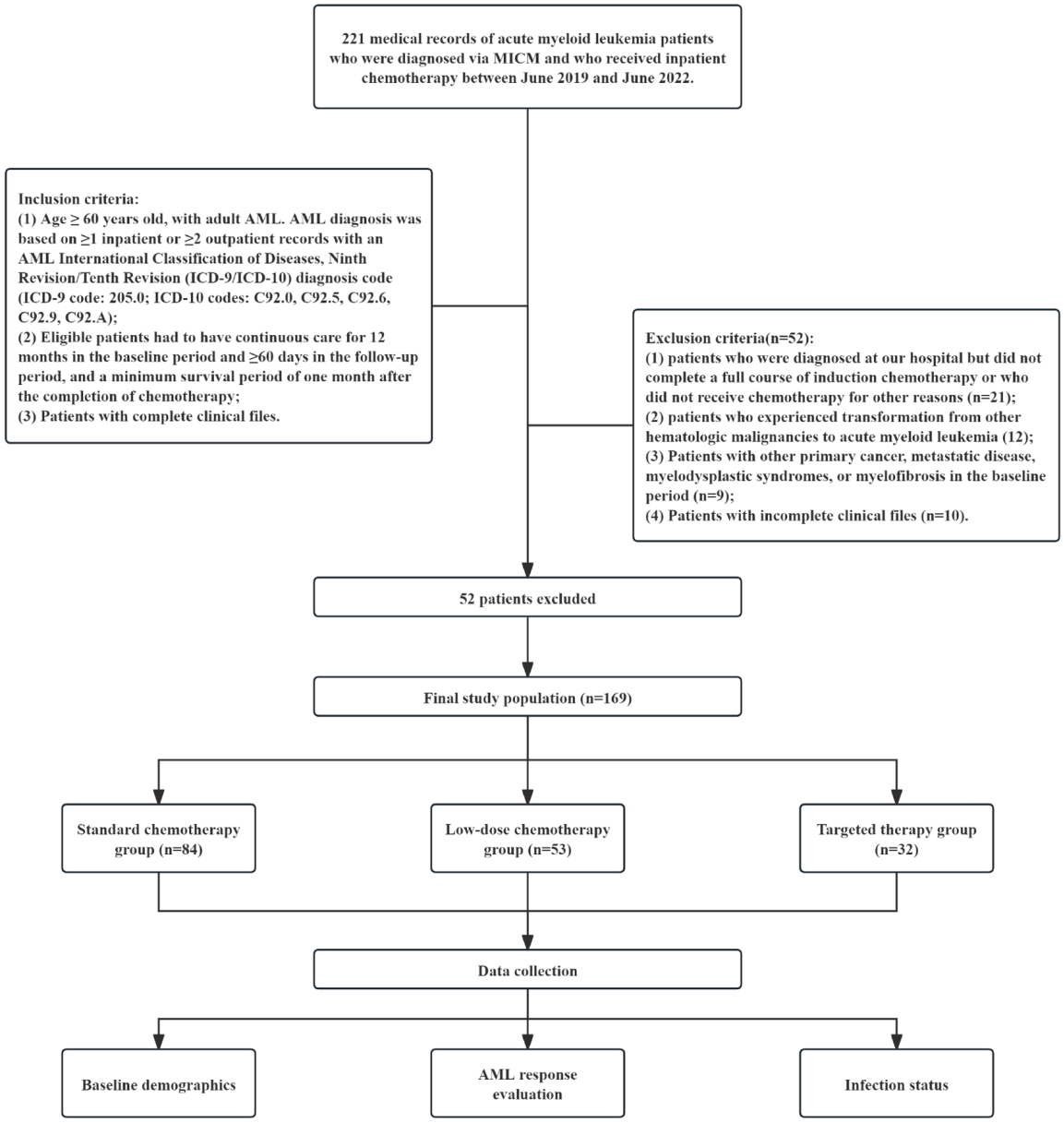

Figure 1. Flow chart of study procedure.

chemotherapy and low-dose chemotherapy. From December 2020, VEN-HMA therapy has become the primary treatment regimen (targeted therapy group). The treatment regimens for the standard chemotherapy group included IA [idarubicin (IDA) + cytarabine (Ara-C)], DA [daunorubicin (DA) + Ara-C], FLAG [fludarabine (FA) + Ara-C + granulocyte colony-stimulating factor (G-CSF)], and MA [mitoxantrone (MIT) + Ara-C]. The low-dose chemotherapy group received low-intensity chemotherapy with treatment regimens such as CAG [cytarabine + aclarubicin (ACR) + G-CSF], HAG [homoharringtonine (HHT) + Ara-C + G-CSF], IAG [IDA + Ara-C + G-CSF], HMA, HMA + CAG, HMA + HAG, and HMA + IAG. The targeted therapy group included patients receiving VEN-HMA treatment, with the specific treatment regimens as follows: VEN at 0.1 g on Day 1, 0.2 g on Day 2, and 0.4 g from Days 4-28. If co-administered with voriconazole or posaconazole, the regimen was adjusted to 0.1-0.2 g from Days 1-28. The HMA agents used were primarily decitabine or azacitidine, with decitabine given at a dose of 20 mg/m^2 from Days 1-7 or azacitidine at 75 mg/m^2 from Days 1-7.

Data extraction

All data were extracted from the patient electronic medical record. Baseline demographics recorded on the index date included age, gender, and comorbidities. Laboratory data for bone marrow blasts, white blood cells, hemoglobin, platelets, albumin during the treatment period and within 30 days in the follow-up period were recorded.

Study outcomes

The primary outcome was the incidence of infections, while AML response served as the secondary outcome. Time to treatment initiation was defined as the period from the index date to the first evidence of chemotherapy during follow-up, and duration of therapy was calculated as the initiation of first-line therapy to the last day of therapy, with an additional 28-day run-out period.

(1) AML response evaluation: AML prognostic stratification and response evaluation were based on the 2017 European LeukemiaNet (ELN) guidelines for the diagnosis and management of adult AML patients [7]. The prognosis is stratified into favorable, intermediate, and adverse. The treatment responses are classified as complete remission (CR), CR with incomplete hematologic recovery (CRi), partial remission (PR), and no response (NR).

(2) Infections: The diagnostic and treatment criteria for neutropenia, fever, and bacterial infections were guided by the *"Clinical Application Guidelines for Antimicrobial Agents in Neutropenic Patients with Fever in China (2020 edition)"* [8]. Neutropenia was defined as an absolute neutrophil count (ANC) $<0.5\times10^9$/L in peripheral blood or an anticipated ANC$<0.5\times10^9$/L within 48 hours. Fever was defined as a single oral temperature ≥38.3°C (axillary temperature ≥38.0°C) or an oral temperature ≥38.0°C (axillary temperature ≥37.7°C) sustained for more than 1 hour. Bacterial infections were primarily diagnosed based on medical history, physical examinations, laboratory tests, and microbiological examinations, such as blood culture and metagenomic next-generation sequencing (mNGS). Imaging examinations such as X-rays and CT scans were used to locate the infection sites.

The diagnosis and treatment of fungal infections followed the *"Diagnosis Criteria and Treatment Principles for Invasive Fungal Diseases in Hematological Malignancies/Malignant Tumors (6th revised edition)"* [9]. The diagnosis of invasive fungal disease (IFD) is divided into four levels: proven, probable, possible, and undetermined. Treatment strategies included prophylactic treatment, empirical treatment, diagnostic-driven treatment, and targeted treatment. Empirical treatment was initiated for persistent neutropenia with fever unresponsive to 4-7 days of broad-spectrum antifungal therapy. Breakthrough invasive fungal disease (bIFD) is defined as a proven/probable IFD that occurs under antifungal prophylactic treatment. Patients initiating antifungal therapy received either targeted treatment, diagnostic-driven treatment, or empirical antifungal treatment.

(3) Septic Shock and i-MODSE: The diagnosis of septic shock followed the *"Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)"* [10]. Septic shock is defined in patients with sepsis who, despite adequate fluid resuscitation, exhibit persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) ≥65 mmHg, along with a serum lactate level >2 mmol/L.

The diagnosis of infection-induced multi-organ dysfunction syndrome in the elderly (i-MODSE) was based on the *"Chinese Expert Consensus on Diagnosis and Treatment of Infection-Induced Multiple Organ Dysfunction Syndrome in the Elderly"* [11], while multiorgan dysfunction was evaluated using the SOFAE (Sequential Organ Failure Assessment for the Elderly) scoring system, where a score of 4 indicates the stage of organ dysfunction.

Statistical analysis

Data analysis was conducted using SPSS 26.0 software. Continuous variables with a normal distribution were expressed as the mean ± standard deviation, and comparison among three groups were conducted using analysis of variance (ANOVA) followed by least significant difference (LSD) t test; Non-normally distributed data were expressed the median (interquartile range), and group comparisons were conducted using the Kruskal-Wallis test. Categorical data were presented as counts or per-

Table 1. Comparison of baseline characteristics among three groups of patients

Characteristics	Targeted Therapy Group (N=32)	Standard Chemotherapy Group (N=84)	Low-Dose Chemotherapy Group (N=53)	*P* value
Age, years, median (IQR)	73 (69, 79)	68 (64, 73)	71 (66, 75)	<0.001
Gender				0.650
Male	19 (59.4)	45 (53.6)	26 (49.1)	
Female	13 (40.6)	39 (46.4)	27 (50.9)	
Comorbidities	28 (87.5)	39 (46.4)	31 (58.5)	<0.001
Bone marrow blasts				0.485
<50%	14 (43.8)	38 (45.2)	29 (54.7)	
≥50%	18 (56.3)	46 (54.8)	24 (45.3)	
WBC, median (IQR) (1×10^9/L)	25.7 (2.6, 25.8)	34.7 (2.5, 55.6)	27.7 (2.6, 25.8)	0.564
PLT, median (IQR) (1×10^9/L)	59 (21, 75)	67 (24, 93)	65 (26, 86)	0.569
HB, median (IQR) (1×10^9/L)	78 (65, 93)	77 (60, 91)	76 (63, 91)	0.854
ALB, mean ± SD (g/L)	35.5±3.7	35.0±5.4	34.3±4.8	0.118
ELN classification				0.431
Favorable	8 (25.0)	30 (35.7)	12 (22.6)	
Intermediate	18 (56.3)	45 (53.6)	33 (62.3)	
Unfavorable	6 (18.8)	9 (10.7)	8 (15.1)	

The data are presented as the number (%) of patients unless otherwise indicated. Abbreviations: WBC, White Blood Cell; PLT, Platelet; HB, Hemoglobin; ALB, Albumin; ELN, European Leukemia Net; IQR, interquartile range.

centage (%), and comparisons were performed using the chi-square test or Fisher's exact test. Multivariate forward stepwise logistic regression analysis was employed to identify independent risk factors for infections, including all independent variables that were statistically significantly in the univariate analysis. A *p* value <0.05 was considered statistically significant.

Results

General characteristics of the patients

From June 2019 to June 2022, a total of 169 elderly AML patients (≥60 years old) were diagnosed via MICM at the First Affiliated Hospital of USTC. The cohort included 84 patients in the standard chemotherapy group, 53 in the low-dose chemotherapy group, and 32 in the targeted therapy group. The patients in the targeted therapy group were significantly older than those in the standard chemotherapy group and the low-dose chemotherapy group (73 years vs. 68 years vs. 71 years, P<0.05). Patients with comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD), coronary heart disease, arrhythmia, myocardial infarction, and cerebral infarction at the time of diagnosis were classified as having underlying disease. The targeted therapy group had a significantly higher proportion of patients with comorbidities than the standard chemotherapy group and low-dose chemotherapy group (87.5% vs. 46.4% vs. 58.5%, P<0.05). No significant differences were observed among the three groups in sex composition, bone marrow morphology, proportions of primitive cells, white blood cell count, platelet count, hemoglobin level, or albumin level at the time of diagnosis among the three groups (all P>0.05). Additionally, a higher proportion of patients with poor prognosis was noted in the targeted therapy group compared to the standard chemotherapy group and the low-dose chemotherapy group (18.8% vs. 10.7% vs. 15.1%, P>0.05) (**Table 1**).

Analysis of the general infection status

Among the 169 elderly AML patients, 79 patients achieved CR/CRi. In the targeted therapy group, 22 patients achieved disease remission, resulting in an overall response rate (ORR) of 68.8%. In the standard chemotherapy group, 43 patients achieved disease remission, with an ORR of 51.2%. In the low-dose chemotherapy group, 14 patients achieved disease remission, resulting in an ORR of 26.4%. The differences among the three groups were statistically significant (P=0.0004, **Table 2**).

Table 2. Overall response rate (ORR) of the patients

	Total (N=169)	Targeted Therapy Group (N=32)	Standard Chemotherapy Group (N=84)	Low-Dose Chemotherapy Group (N=53)
CR/CRi	79	22	43	14
ORR (%)	46.7	68.8	51.2	26.4
P		0.0004		

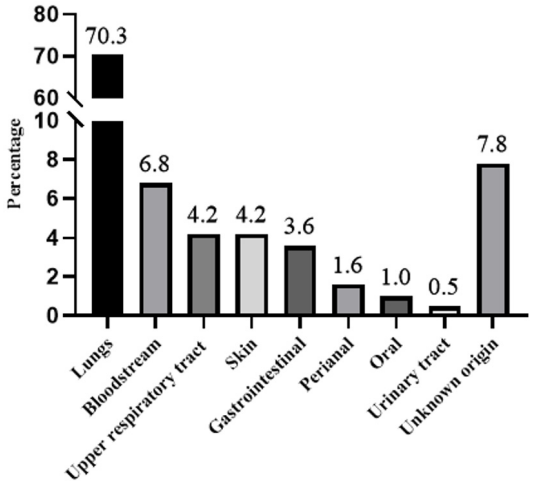

Figure 2. Distribution of infection sites during initial induction chemotherapy in elderly AML patients. Abbreviation: AML, acute myeloid leukemia.

The duration of neutropenia in the targeted therapy group was 9.0±8.4 days, significantly shorter than 15.0±15.0 days and 9.3±9.1 days in the other two groups (P<0.05). The duration of fever in the targeted therapy group was 2.34±3.59 days, also significantly shorter than the 4.52±4.38 days and 3.53±4.76 days in the standard chemotherapy group and the low-dose chemotherapy group (P<0.05).

Of the 169 elderly AML patients, 158 patients experienced infections during the initial induction chemotherapy, with a total of 192 infection episodes and an overall infection rate of 93.5%. Infections affected single or multiple sites, with lung infections being the most common (70.53%), followed by bloodstream infections, upper respiratory tract infections, skin infections, gastrointestinal infections, perianal infections, oral infections, urinary tract infections, and infections of unknown origin (**Figure 2**). In the targeted therapy group, 28 patients experienced infections, with an infection rate of 87.5%. In the standard chemotherapy group, 80 patients experienced infections, resulting in an infection rate of 95.2%. In the low-dose chemotherapy group, 50 patients experienced infections, with an infection rate of 94.3%. The incidence of infections was lowest in the targeted therapy group (P<0.05).

Bacteremia infection status

Among the 169 elderly AML patients, 158 patients experienced infections during the initial induction chemotherapy, with a total of 192 infection episodes. Blood cultures or second-generation pathogen sequencing identified 23 bacterial strains, including 18 strains (78.3%) of gram-negative bacteria (G-) accounting. The most common G- bacterium was *Escherichia coli*. There were 5 strains (21.7%) of gram-positive bacteria (G+), including *Staphylococcus aureus* and *Enterococcus* species (**Table 3**).

Analysis of risk factors for bacterial infections

Univariate analysis revealed significant differences between patients who experienced infections and those who did not in terms of chemotherapy regimens, neutropenic status, duration of neutropenia, and duration of fever (all P<0.05). These significant indicators were included in a multivariate logistic regression model for further analysis. The results identified neutropenic state and the duration of fever as independent risk factors for bacterial infections during initial induction chemotherapy in elderly AML patients (all P<0.05) (**Table 4**).

Prevention and treatment of fungal infections

Among the 169 elderly AML patients undergoing induction therapy, 76 patients received preemptive antifungal prophylaxis (AFP). The AFP distribution was as follows: 15 (46.8%) out of 32 patients in the targeted therapy group, 39 (46.4%) out of 84 patients in the standard chemotherapy group, and 22 (41.5%) out of 53 patients in the low-dose chemotherapy group (P>0.05). Of the total cohort, 75 patients ultimately initiated antifungal treatment, including 11 patients (34.4%) in the targeted therapy

Table 3. Distribution of pathogenic bacteria in bacteremia infections

Pathogenic Bacteria	Strain Count (N=23)	Ratio (%)
G-	18	78.3
Escherichia coli	5	21.7
Stenotrophomonas maltophilia	4	17.4
Klebsiella pneumoniae	2	8.7
Pseudomonas aeruginosa	2	8.7
Bacteroides fragilis	2	8.7
Enterobacter aerogen	1	4.3
Acinetobacter baumannii	1	4.3
Acinetobacter sunderella	1	4.3
G+	5	21.7
Staphylococcus aureus	3	13.0
Enterococcus species	2	8.7

Abbreviations: G-, gram-negative bacteria; G+, gram-positive bacteria.

group, significantly lower than 41 patients (48.8%) in the standard chemotherapy group, and 23 (43.4%) patients in the low-dose chemotherapy group, as shown in **Figure 3**. There was no significant difference in the proportion of patients who initiated antifungal treatment between those who achieved complete remission (CR/CRi) and those who did not achieve remission (36.7% vs. 51.1%, P>0.05).

Fungal infections and breakthrough cases

Of the 169 patients, 15 patients (8.9%) were clinically diagnosed or confirmed with IFD, including 7 bIFD cases. A total of 10 fungal strains were isolated, including species of *Aspergillus* (including *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus nidulans*), 2 strains of *Candida albicans*, and others, such as *Scopulariopsis brevicaulis*, *Mucor miehei*, *Fusarium solani*, and *Rhizopus species*.

Analysis of risk factors for fungal infections

All patients who initiated antifungal treatment were included in the univariate analysis and binary logistic regression analysis. The results showed that in elderly AML patients undergoing initial induction chemotherapy, the occurrence of IFD was associated with the chemotherapy regimen, neutropenic status, duration of neutropenia, and duration of fever but not related to AFP. Among these factors, receiving nontargeted therapy, duration of neutropenia, and duration of fever were identified as independent risk factors for IFD (all P<0.05). Additionally, further subgroup analysis within the targeted therapy and traditional chemotherapy groups (standard chemotherapy group and low-dose chemotherapy group) showed that AFP did not significantly impact the occurrence of IFD in either group (P>0.05) (**Table 5**).

Occurrence of septic shock and i-MODSE

Among the 169 elderly AML patients, only one patient experienced septic shock, and two patients progressed to the functional failure stage of i-MODSE. These three patients were in the standard chemotherapy group. Due to the small sample size, statistical analysis was not performed.

Discussion

Acute myeloid leukemia (AML) is the most prevalent type of acute leukemia in adults. While advances in intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT) has improved the survival rates in AML patients, these approaches are limited to younger patients and those without high-risk cytogenetic profiles. For elderly AML patients, treatment options are often limited due to factors such as advanced age, frailty, and comorbidities [12]. Several domestic and international studies have shown that the long-term survival rate in newly diagnosed elderly AML patients is only 5%-20%, with an even worse prognosis for those in the adverse-risk groups defined by the European LeukemiaNet (ELN) [13]. Venetoclax (VEN), a selective oral Bcl-2 inhibitor, induces apoptosis in malignant cells dependent on Bcl-2. VEN targets AML cells more precisely with minimal adverse effects on normal cells [14]. VEN has been approved in combination with hypomethylating agents, such as azacitidine or decitabine, for newly diagnosed AML patients who are unsuitable for intensive chemotherapy, excluding patients with acute promyelocytic leukemia. In addition, a real-world study showed that decitabine + VEN treatment had a better and faster treatment response than DEC monotherapy in newly

Table 4. Univariate and multivariate analyses of risk factors for bacterial infections during initial induction therapy in elderly AML patients

Variables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Nontargeted therapy	0.377 (0.103-1.376)	0.041	-	-
Neutropenic status	6.384 (1.808-22.537)	0.004	6.065 (1.153-31.910)	0.033
Duration of neutropenia	1.067 (0.988-1.152)	0.038	-	-
Duration of fever	1.958 (1.090-3.518)	0.025	1.895 (1.048-3.426)	0.034

Abbreviations: OR, odds ratio; CI, confidence interval.

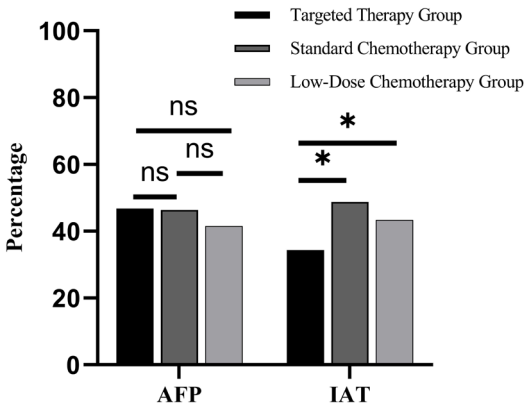

Figure 3. Comparison of patients undergoing preemptive antifungal prophylaxis and antifungal therapy for IFD among the three groups. ns, no statistical significance; *, P<0.05. Abbreviations: AFP, antifungal prophylaxis; IAT, initial antifungal therapy; IFD, invasive fungal disease.

diagnosed elderly AML patients, improving OS and event free survival (EFS) without affecting length of hospitalization or transfusion rates [15].

Regardless of whether traditional chemotherapy or targeted treatment, such as VEN-based regimens, is adopted, AML patients experience inevitable bone marrow suppression during induction therapy. Additionally, AML patients have functional defects in their granulocytes, making them at high risk for infection [16]. Previous literature reports that 95% of patients have at least one episode of febrile neutropenia and/or documented infection (clinical or microbiological) during induction chemotherapy, with an average of 1.4 infections per patient during this period [17, 18]. In a multicenter clinical trial conducted by the Acute Leukemia French Association (ALFA)-9802 [19], which included 459 adult AML patients, a total of 1369 febrile events were observed, including fever of unknown origin (23%) and clinically or microbiologically documented fever (77%). Only 22 patients (5%) did not experience any febrile event during induction therapy. Furthermore, compared with other treatment cycles, pulmonary infections were notably more common during induction, with nearly all bacterial pneumonia cases caused by gram-negative bacteria. Several domestic studies have also shown that nosocomial infection rates in AML patients exceeds 60%, primarily affecting the lungs and upper respiratory tract [20, 21]. In this study, the infection rate among all elderly AML patients was 93.5%, with infection site distribution and pathogen profiles aligning closely with current findings.

Compared to traditional chemotherapy regimens, VEN targets specific pathways in leukemia cells, resulting in higher and faster response rates with fewer adverse reactions, such as shorter neutropenic duration, minimal impact on organ function, and reduced likelihood of triggering inflammatory reactions. Therefore, the introduction of targeted therapy has the potential to reduce infection rates in leukemia patients with compromised immune function. Zhu et al. [22] found that compared with conventional chemotherapy, the incidence of infectious complications significantly decreased with venetoclax combined with decitabine or azacitidine. A study conducted in 2019 reported the safety and efficacy of VEN combined with hypomethylating agents (VEN-HMA) for newly diagnosed elderly AML patients unfit for intensive chemotherapy [23]. Involving 145 patients (median age: 74 years) with a median follow-up time of 8.9 months, the study found an overall CR/CRi rate of 67%, rising to 73% in the VEN-HMA cohort, reflecting good tolerability. Subsequently, another study in 2021 compared the VEN-HMA efficacy with intensive chemotherapy in elderly AML patients [24],

Table 5. Univariate and multivariate analysis of risk factors for fungal infection during initial induction therapy in elderly AML patients

Variables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Antifungal prophylaxis	0.635 (0.219-1.845)	0.404	-	-
Nontargeted therapy	0.636 (0.136-2.970)	0.046	1.011 (0.194-5.262)	0.009
Neutropenic status	3.387 (0.428-26.777)	0.024	-	-
Duration of neutropenia	1.088 (1.026-1.154)	0.005	1.072 (1.002-1.147)	0.043
Duration of fever	1.111 (1.008-1.225)	0.035	1.076 (0.963-1.203)	0.019

Abbreviations: OR, odds ratio; CI, confidence interval.

reporting CR/CRi rates of 81% for VEN-HMA versus 52% for intensive chemotherapy. This finding highlights VEN-HMA as a more effective treatment option. On the other hand, in a randomized placebo-controlled phase III trial conducted in 2016, VEN combined with azacitidine was used to treat newly diagnosed AML patients aged ≥75 years who were unfit for intensive chemotherapy. The study revealed that 84% of patients experienced any grade of infection, demonstrating a decreased infection rate compared with traditional chemotherapy approaches [25]. In this study, despite the older age and higher comorbidity rate in the targeted therapy group, they achieved a significantly higher induction remission rate (68.8% vs. 51.2% vs. 26.4%) and a lower infection rate (87.5% vs. 95.2% vs. 94.3%) than the other two groups, consistent with prior research findings [24, 26, 27]. These data suggest that compared with chemotherapy alone, targeted treatment regimens significantly improve the remission rate in elderly AML patients while maintaining good tolerability, establishing them as a safe and effective treatment option [28].

Multiple studies, both domestic and international, have revealed various risk factors contributing to infections during induction therapy in AML patients. These factors include advanced age, high-intensity chemotherapy, prolonged duration of neutropenia, and prophylactic use of antimicrobial agents [19, 21, 29]. In this study, the enrolled patients were all elderly individuals (median age of 70 years), making it challenging to establish a correlation between advanced age and infection among the three groups. The results revealed that neutropenic state and prolonged duration of fever were independent risk factors for infection, aligning with current research findings. Additionally, the incidence of infection-related shock or multiple organ failure observed in this study was similar to rates reported in previous studies [30, 31], with affected patients primarily in the standard treatment group. However, due to the limited sample size, this study was unable to establish a definitive correlation between these outcomes and treatment regimens.

IFD is a common complication in AML patients undergoing intensive induction chemotherapy and is one of the significant causes of morbidity and mortality [32]. AFP is typically used in standard treatment regimens, but its necessity remains controversial in AML patients receiving VEN-based therapy. Previous studies suggest that AFP does not affect the incidence of IFD in AML patients [33, 34]. Moreover, interactions between VEN and azole drugs can result in severe adverse reactions, potentially impacting patient outcomes. In this study, the overall incidence of diagnosed/clinically diagnosed IFD was 8.9%, comparable to the 8% incidence observed by DiNardo et al. [35] in a dose escalation and expansion study of VEN-HMA, where 46% of patients received AFP. Our study found no significant correlation between AFP use and IFD occurrence, regardless of whether the patients received targeted therapy or traditional chemotherapy, with IFD rates of 3.8% and 4.3%, respectively. This result suggests that even without AFP, the incidence of IFD remains low. On the other hand, compared with patients receiving traditional chemotherapy, a significantly lower proportion of patients in the targeted therapy group initiated antifungal treatment, which was associated with shorter durations of neutropenia and fever in the targeted therapy group, regardless of the use of AFP, consistent with previous reports by Chen et al. [34]. In the study by Chen et al., involving 131 newly diagnosed AML patients undergoing frontline VEN-HMA treatment, AFP had no

impact on IFD incidence, indicating that AFP may be unnecessary for patients on VEN-based regimens when IFD risk is low. Interestingly, complete remission rates were significantly lower in the AFP group (9.1%) compared to the non-AFP group (39%) (P=0.046), suggesting that the need to reduce VEN dosage when co-administered with azole antifungals may negatively affect remission outcomes [35]. Consequently, the combination of AFP and VEN dose reduction is not recommended. Compared to patients who did not develop IFD, those who initiated antifungal treatment had a slightly lower complete remission rate after induction therapy (53.2% vs. 38.7%), but the difference was not statistically significant. Given that prolonged neutropenia is an independent risk factor for IFD, achieving complete remission to restore immune system function and reducing the duration of neutropenia may be essential in preventing IFD in elderly AML patients [36].

Conclusion

In summary, compared with standard and low-dose chemotherapy, targeted therapy combing VEN and HMA improves disease remission rates in elderly AML patients. Additionally, the targeted therapy has a favorable safety profile, with a lower incidence and severity of infections. However, the occurrence of IFD during initial induction therapy in elderly AML patients remains to be studied. In this study, antifungal prophylaxis did not affect the incidence of IFD in elderly AML patients, and the overall incidence of diagnosed/clinically diagnosed IFD was low, regardless of antifungal prophylaxis use. This study provides some evidence for guiding the treatment of elderly AML patients. However, as a single-center study with a limited sample size and short follow-up, this study has inherent limitations, and further research is warranted.

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Disclosure of conflict of interest

None.

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