https://doi.org/10.46765/2675-374X.2025v7n1e315 ORIGINAL ARTICLE

Real-world outcomes of BCL2 inhibitor-based combination therapy in myelodysplastic syndrome and acute myeloid leukemia – Experience from a university hospital in northeastern Brazil

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Section editor: Abrahão Elias Hallack Neto

Received: Nov. 21, 2025 • **Accepted:** Feb. 23, 2026

ABSTRACT

Acute myeloid leukemia (AML) and high-risk myelodysplastic neoplasms (MDS) predominantly affect elderly patients who are often ineligible for intensive chemotherapy. The emergence of BCL2 inhibitors, particularly venetoclax, has changed the therapeutic landscape in these populations when combined with hypomethylating agents or low-dose cytarabine. This study aims to describe the clinical and epidemiological characteristics, treatment patterns, and outcomes of patients with AML and high-risk MDS treated with venetoclax-based regimens at a university hospital in northeastern Brazil. The methodology consists of a retrospective, descriptive study including patients aged ≥ 18 years diagnosed from January 2020 to October 2025. Twenty-six patients were included (19 AML, seven MDS), with a median age of 65 years (range: 37-81). Among AML cases, 42.1% were *de novo* and 57.9% were secondary, mostly post-MDS. Overall, 46.1% achieved complete remission, and 3.8% achieved partial remission. The median time to best response was one cycle. Three patients (11.5%) underwent allogeneic hematopoietic stem cell transplantation. Hematologic toxicity was universal, with febrile neutropenia in 78.3%. Venetoclax-based regimens demonstrated response rates comparable to international real-world data in AML and high-risk MDS, even with shorter venetoclax duration. Frailty remains the main barrier to transplantation, highlighting the importance of expanding access to targeted therapies within the public health system.

Keywords: Acute myeloid leukemia; Myelodysplastic syndrome; BCL2 inhibitor.

INTRODUCTION

Within the World Health Organization (WHO) classification of myeloid neoplasms, myelodysplastic neoplasms (MDS) and acute myeloid leukemias (AML) are prominently featured. As these conditions are more prevalent among the elderly population, the use of less intensive treatment regimens has been increasingly investigated, considering the ineligibility of many patients for high-intensity therapies. In recent years, BCL2 inhibitors (iBCL2) have emerged as a key therapeutic class in diseases such as chronic lymphocytic leukemia (CLL), and their potential applications in AML have been explored through combination therapies.[1-4]

In these neoplasms, tumor cells commonly overexpress BCL2, leading to blockade of apoptotic signaling pathways and resulting in "immortalization" of the clonal population. The mechanism of iBCL2 agents involves inhibition of this signaling cascade, promoting apoptosis via BH3-mimetic molecules, the main representative being venetoclax.[5]

In this context, venetoclax-based therapies have been increasingly incorporated into clinical practice, particularly following the study by DiNardo et al.,[4] which demonstrated that the combination of azacitidine (a hypomethylating agent) and venetoclax maximized overall response rates in AML patients unfit for intensive chemotherapy. In resource-limited settings, the combination of low-dose cytarabine (LDAC) and venetoclax, as reported by Wei et al.,[6] has also gained relevance, especially considering the limited access to novel drugs within the Brazilian Unified Health System (SUS).[4]

In high-risk MDS, evidence regarding the use of azacitidine and venetoclax combination therapy remains scarce, with Phase III trials such as VERONA still ongoing. However, phase Ib studies have reported encouraging overall response rates compared with hypomethylating monotherapy, supporting adoption of this approach in high-risk MDS.[7]

Most major genetic stratification studies in AML have been conducted in patients under 60 years of age, including the widely used European LeukemiaNet (ELN) classification. Accordingly, some authors have proposed models better suited to elderly populations. In 2024, ELN itself published a new genetic risk stratification specifically designed for patients receiving low-intensity regimens, incorporating mutations such as NPM1, IDH1/2, RAS family, FLT3, and TP53.[8,9]

The present study was conducted at a university referral center for the management of hematologic diseases, including hematopoietic stem cell transplantation (HSCT), with a special focus on myeloid malignancies and the inclusion of elderly patients.

To better characterize the treated population, this study aims to describe the main clinical and epidemiological features of patients managed at this university hospital with hypomethylating agents or LDAC in combination with venetoclax for AML and high-risk MDS.

MATERIALS AND METHODS

This was a retrospective, observational, and descriptive study evaluating clinical and epidemiological aspects of patients with high-risk MDS and AML treated at Departamento de Hematologia e Hemoterapia, Hospital Universitário Walter Cantídio, in northeastern Brazil.

Patients aged 18 years or older, diagnosed from January 2020 to October 2025, were included. Diagnoses were established according to the WHO classification, and data collection was performed through review of institutional medical records. Response assessments were conducted using the 2023 International Working Group criteria for MDS and the 2022 ELN criteria for AML.

Statistical analyses and graph generation were performed using R software (version 4.3.2). Overall survival (OS) was estimated using the Kaplan-Meier method.

The study was approved by the Research Ethics Committee of Walter Cantídio University Hospital and registered on Plataforma Brasil under Certificate of Ethical Appreciation number 87047725.1.0000.5045.

RESULTS

During the analyzed period, 19 patients with AML and seven patients with high-risk MDS were included, totaling 26 patients. The median age at diagnosis was 65 years (range: 37-81 years), and most were female (57.6%), as shown in Table 1.

Among the 26 patients, 20 (76.9%) presented with at least one comorbidity, most commonly hypertension and/or type 2 diabetes mellitus, present in 17 of them (75%). Two patients had a prior history of malignancy (one with follicular lymphoma and another with breast cancer). Thirteen patients (50%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and 13 (50%) had ECOG 2. None had ECOG 3.

Table 1. Baseline clinical and demographic characteristics of the patients.

Characteristics	Cohort (n = 26)
Median age (range)	65 (37-81)
Female (%)	15 (57.6)
AML (%)	19 (73.0)
De novo	8/19 (42.1)
Secondary	11/19 (57.9)
Secondary AML (%)	
MDS	7/11 (63.6)
Chronic myelomonocytic leukemia	2/11 (18.2)
Polycythemia vera / primary myelofibrosis	2/11 (18.2)
MDS (%)	7 (27.0)
LB	2/7 (28.6)
IB1	1/7 (14.3)
IB2	4/7 (57.1)
ECOG (%)	
0-1	13/26 (50.0)
2	13/26 (50.0)
Risk stratification (AML) (%)	
Favorable	1/19 (5.3)
Intermediate	16/19 (84.2)
Adverse	2/19 (10.5)
R-IPSS (MDS)	6 (5-10)
Complete blood count at diagnosis	
Hemoglobin (g/dL)	7.01 (4.23-11.30)
Neutrophils (n/mm^3)	1,130 (50-40.960)
Blasts (n/mm^3)	574 (0-300.675)
Platelets (n/mm^3)	35,070 (14.330-383.000)

Source: Elaborated by the authors.

Among AML cases, eight (42.1%) were *de novo* and 11 (57.9%) were secondary. The main preceding condition was MDS (seven cases, 63.6%), but there were also patients with chronic myelomonocytic leukemia, polycythemia vera, and primary myelofibrosis. According to the ELN risk classification, 16 (84.2%) were intermediate risk, two (10.5%) adverse risk, and one (5.3%) favorable risk.

Most high-risk MDS cases were classified as MDS with excess blasts – five out of seven patients (69.4%) – with a median Revised International Prognostic Scoring System (R-IPSS) score of 6 (range: 5-10).

Half of the patients were treated with an azacitidine-based regimen and half with LDAC; two patients who were initially treated with LDAC switched to azacitidine after two cycles due to medication availability.

Among patients treated for AML, four (21%) had received at least one previous line of therapy, while the remaining were treated with venetoclax-based regimens as first-line therapy.

The median number of treatment cycles was three (range: 1-10). The best overall response achieved was complete remission (CR) in 12 patients (46.1%) and partial remission (PR) in one patient (3.8%), while the remaining patients were refractory (38.4%). The median time to best response was one cycle (range: 1-7), including one AML patient who achieved CR after five cycles and one high-risk MDS patient who achieved CR after seven cycles.

Among the 19 AML patients, eight achieved CR (42.1%), one achieved PR (5.3%), eight were refractory (42.1%), and two (10.5%) did not undergo response assessment after therapy (presumed refractory).

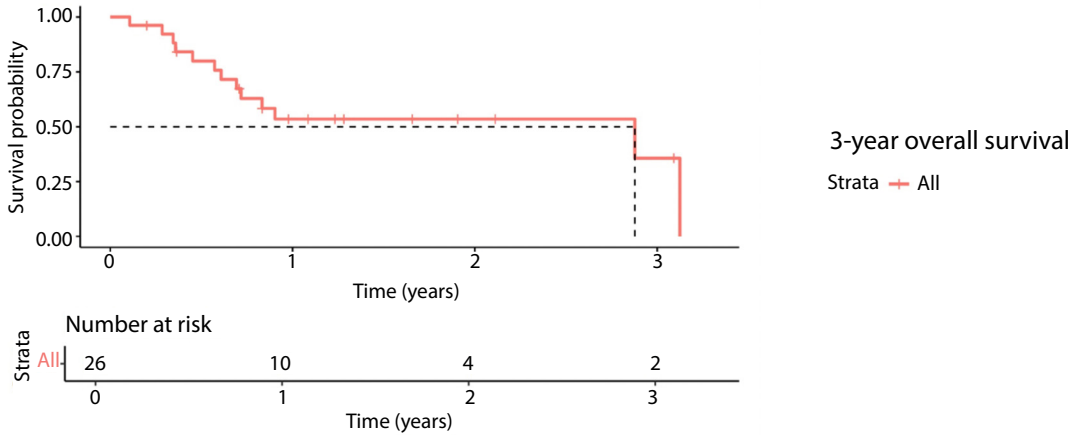
Among the high-risk MDS patients, four achieved CR (57.1%), two were refractory (28.5%), and one did not have a documented response evaluation during follow-up. Treatment characteristics were summarized in Table 2.

Table 2. Treatment characteristics.

Treatment characteristics	
Treatment	
LDAC + venetoclax	13/26 (50%)
Azacitidine + venetoclax	13/26 (50%)
Median cycles	3 (1-10)
Best response	
CR	12/26 (46.1%)
PR	1/26 (3.8%)
Refractory	10/26 (38.4%)
Time to best response (cycles)	1 (1-7)
Dose management	
Initial dose (mg)	400 (100-400)
Concomitant azole	15/26 (57.6%)
Duration (days)	14 (7-28)
Reduction	4/26 (15.3%)
Increase	4/26 (15.3%)
Transfusion independence	
In 3 months	8/16 (50.0%)
In 6 months	7/14 (50.0%)
Allogeneic HSCT	3/26 (11.5%)
Contraindications to HSCT	
Refractoriness	5/22 (22.8%)
Relapse	3/22 (13.6%)
Frailty	10/22 (45.4%)
No information	4/22 (18.2%)

Source: Elaborated by the authors.

The cohort 2-year OS was 53%, with a median survival of 1,051 days. When analyzed by diagnosis, AML patients had a 2-year OS of 41% with a median of 304 days, while high-risk MDS patients had a 2-year OS of 83% with a median of 1,141 days, as seen in Fig. 1 and 2.

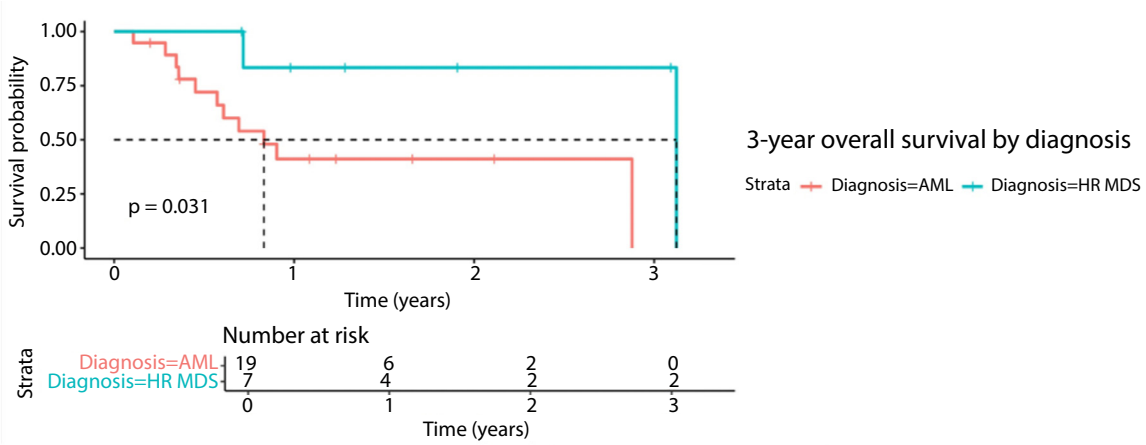


Characteristic	1y	2y	3y
Overall	53% (37%, 78%)	53% (37%, 78%)	36% (15%, 86%)

Characteristic	Median survival
Overall	1,051 days

Source: Elaborated by the authors.

Figure 1. Three-year OS and median survival.



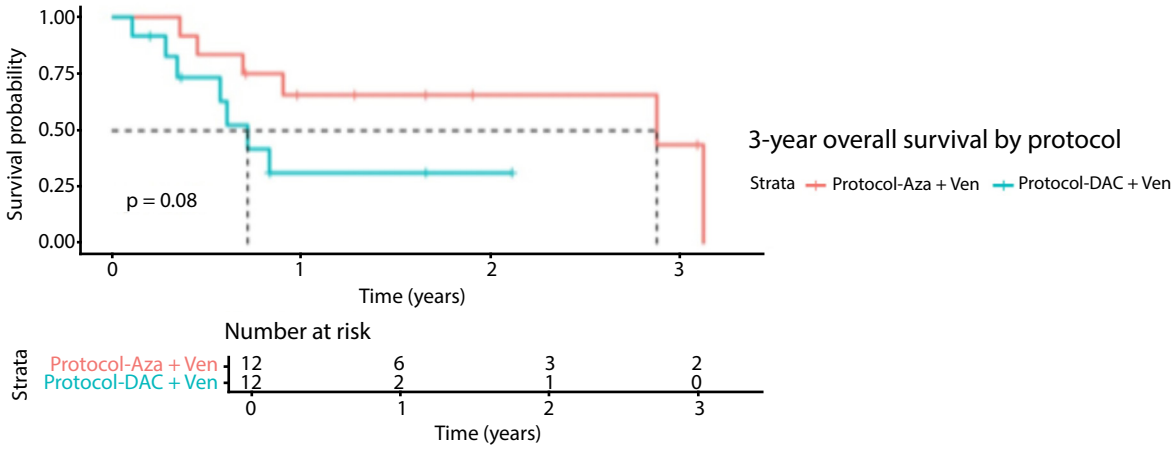
Characteristic	1y	2y	3y
Diagnosis			
AML	41% (23%, 73%)	41% (23%, 73%)	– (–, –)
HR MDS	83% (58%, 100%)	83% (58%, 100%)	83% (58%, 100%)

Characteristic	Median survival
Diagnosis	
AML	304 days
HR MDS	1,141 days

Source: Elaborated by the authors.

Figure 2. Three-year OS and median survival by diagnosis.

According to the treatment regimen, survival also differed: median OS was 1,051 days for azacitidine plus venetoclax versus 262 days for LDAC plus venetoclax, as seen in Fig. 3.



Characteristic	1y	2y	3y
Protocol			
Aza + Ven	66% (43%, 100%)	66% (43%, 100%)	44% (18%, 100%)
LDAC + Ven	31% (12%, 79%)	31% (12%, 79%)	– (–, –)

Characteristic	Median survival
Protocol	
Aza + Ven	1,051 days
LDAC + Ven	262 days

Source: Elaborated by the authors.

Figure 3. Three-year OS and median survival by protocol.

The most frequently used venetoclax dose was 400 mg (range: 100-400 mg), with 15 patients (57.6%) receiving concomitant azole antifungal therapy, implying dose reductions due to drug interactions. The median venetoclax duration per cycle was 14 days (range: 7-28 days), with dose duration adjustments in eight patients; four (15.3%) had their duration increased, and four (15.3%) had it reduced as a dose adjustment strategy.

Among 16 evaluable patients at 3 months, eight (50%) achieved transfusion independence; at 6 months, seven (50%) of the 14 evaluable patients were transfusion independent.

Of the 26 patients, only three (11.5%) underwent allogeneic HSCT (allo-HSCT), all of whom had high-risk MDS. One additional patient was undergoing HSCT evaluation at the time of manuscript preparation, and 22 were deemed ineligible for the procedure.

The main reason for ineligibility was frailty (45.4%), followed by refractory disease (22.8%) and disease relapse (13.6%). In four patients (18.2%), the reason for ineligibility was not documented.

Regarding adverse events, hematologic toxicities were assessed. Among 23 patients with toxicity data, all (100%) presented with anemia and neutropenia – 18 (78.3%) of whom developed febrile neutropenia – and 19 (82.6%) experienced thrombocytopenia. Most adverse events were grade 3-4, as shown in Table 3.

Table 3. Hematologic adverse events.

Event	All grades	Grade 3/4
Anemia	23/23 (100.0%)	21/23 (91.3%)
Neutropenia	23/23 (100.0%)	22/23 (95.6%)
Febrile neutropenia	18/23 (78.3%)	18/23 (78.3%)
Thrombocytopenia	19/23 (82.6%)	17/23 (73.9%)

Source: Elaborated by the authors.

DISCUSSION

Therapeutic strategies for the management of myeloid malignancies in unfit patients have evolved in recent years with the advent of targeted agents and their combination with hypomethylating therapies. Already approved for use in AML, the combination of azacitidine and venetoclax has also been increasingly employed off-label in the treatment of high-risk MDS. The remission and survival outcomes in our cohort are comparable to those reported in previous studies.[4,6,7,10]

In the AML setting, our results were consistent with those observed in the pivotal azacitidine plus venetoclax trial, showing a CR rate of 42.1%, despite a substantial proportion of our patients having been treated with a less effective regimen according to the literature (LDAC-based) and with a higher percentage of secondary AML cases.[4,6] In the MDS setting, where available data come primarily from retrospective studies, CR rates were similarly high at 57.1%.[7,10]

The rapid achievement of response (median of one cycle) reinforces the role of venetoclax as a sensitizer to hypomethylating agents and low-intensity chemotherapy, as demonstrated in other cohorts.[4,6]

As expected, survival outcomes were statistically significantly different between AML and high-risk (HR) MDS patients, with OS among AML cases exceeding that reported in the VIALE-C trial, despite most patients having received LDAC plus venetoclax. When comparing outcomes by treatment regimen, patients who switched protocols were excluded from analysis; however, confounding factors persisted, as all HR MDS patients received azacitidine-based regimens. Consequently, survival by protocol showed a nearly fivefold difference in median survival in favor of azacitidine plus venetoclax.[4,6]

Despite outcomes comparable to the literature, it is noteworthy that our cohort showed a shorter median venetoclax duration (14 days), below the standard 28 days typically used in protocols, along with a high rate of concomitant azole antifungal use requiring dose reduction due to pharmacologic interactions. This finding aligns with discussions in recent publications suggesting that shortening venetoclax duration may mitigate adverse effects, particularly hematologic toxicity, without compromising efficacy.[11,12]

Nonetheless, hematologic toxicity was universal, with higher rates than those reported in pivotal LDAC or azacitidine plus venetoclax trials, despite the aforementioned dose and duration adjustments.

Although a high proportion of patients achieved CR in both disease groups, only three individuals – all with HR MDS – underwent allo-HSCT, which remains the only curative strategy for this population. It is worth emphasizing that recent studies have questioned the need for achieving CR prior to HSCT in MDS patients.

The main reason for transplant ineligibility in our series was frailty, which has been increasingly recognized in the literature as a key determinant for HSCT candidacy, often outweighing chronological age.[13-16]

This study faced analytical challenges due to incomplete data in medical records and to our sample size. There also might have been interferences in the results due to access limitation issues and to the socioeconomic status of the patients. Despite limitations inherent to its retrospective design, our findings reflect real-world practice at a public university center, contributing to the national landscape regarding the use of iBCL2 in myeloid diseases.

CONCLUSION

AML and HR MDS remain conditions associated with high morbidity and mortality, particularly among elderly patients, due to therapeutic limitations within the public healthcare system. Frailty continues to represent the main barrier to allo-HSCT.

The use of iBCL2, such as venetoclax, has shown potential to improve clinical outcomes even in real-world settings, with dose and duration reductions, allowing patients to proceed to allo-HSCT, in our cohort of HR MDS patients. The reduced-duration use of venetoclax is feasible and should continue to be studied as a way to mitigate severe adverse events. Prospective studies are warranted to further define and consolidate the role of these agents in this context.

CONFLICTS OF INTEREST

Nothing to declare.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors declare that no artificial intelligence tools were used in the preparation, writing, data analysis, or review of this manuscript.

FUNDING

This research did not receive any specific funding from public, commercial, or not-for-profit funding agencies.

DATA AVAILABILITY STATEMENT

All data were analyzed in this study.

AUTHOR'S CONTRIBUTIONS

Conceptualization: Oliveira GM; Duarte FB. **Investigation:** Oliveira GM; Vasconcelos ETMFS; Rocha MLFC; Cunha FM. **Methodology:** Oliveira GM. **Formal Analysis:** Oliveira GM; Segundo HAM. **Data Curation:** Oliveira GM; Vasconcelos ETMFS; Rocha MLFC; Cunha FM. **Project Administration: Funding Acquisition: Writing:** Oliveira GM. **Supervision:** Duarte FB. **Final Approval:** Oliveira GM.

ACKNOWLEDEGEMENTS

Not applicable.

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