

LEUKEMIA

Navigating a Paradigm Shift Venetoclax Treatment Redefines Landscape of Acute Myeloid Leukemia

ABSTRACT

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by the accumulation of malignant myeloid progenitor hematopoietic cells in the bone marrow and peripheral blood. Recent studies have shown promising results with the use of small molecule inhibitors and targeted therapy in the treatment of patients with AML. One such molecule is venetoclax, which has been approved in AML by the FDA in combination with hypomethylating agents or low-dose cytarabine. We thoroughly searched electronic literature related to venetoclax and its role in AML, using databases such as MEDLINE, PubMed, Google Scholar, and PsychInfo, through April 2024. We applied population, intervention, comparison, and outcome criteria, specifically focusing on studies with a population using venetoclax from review articles and clinical trials. All selected studies were required to be in English, and any study that did not involve the use of venetoclax was excluded. A meticulous literature review was conducted to consolidate the current knowledge and new combination therapies on AML. In our review article, we focused on the latest advances in the treatment of patients with AML. Based on the literature, we recommend that physicians prioritize the use of venetoclax in the management of this deadly disease because it has been shown to significantly impact the course of the disease.

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by the accumulation of malignant myeloid progenitor hematopoietic cells in the bone marrow and peripheral blood. It primarily affects older people, with a median age at diagnosis of 68 years. Men are 1.5 times more commonly affected than females with an overall incidence of 4 per 100,000 per year.¹ Currently, patients with newly diagnosed AML are treated with the standard regimen, which consists of cytarabine and an anthracycline followed by consolidation therapy with cytarabine or stem cell

transplantation, depending on patient and disease characteristics.² However, older patients and patients with comorbidities cannot tolerate intensive induction chemotherapy and are offered only supportive and palliative treatment. As a result, the long-term cure rates of AML in the older population have historically been as low as 5% to 20%.³

Recent studies have shown promising results with the use of small molecule inhibitors and targeted therapy in the treatment of AML. One such molecule is venetoclax, which was initially

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approved by the FDA for the treatment of chronic lymphocytic leukemia (CLL) in 2016. It since has been approved in combination with hypomethylating agents (HMA) or low-dose cytarabine (LDAC) for AML in patients who are previously untreated, are older, or cannot tolerate intensive chemotherapy. More recently venetoclax was approved for refractory multiple myeloma. It has also shown encouraging results for other hematological malignancies, especially lymphomas.⁴⁻⁸

Methodology

Our team conducted a thorough search for electronic literature related to venetoclax in multiple databases, including MEDLINE, PubMed, Google Scholar, and PsychInfo, through April 2024. We used keywords such as venetoclax and AML to find relevant studies. The first author carried out independent research, while the first and second authors evaluated the titles, abstracts, and reference lists according to specific eligibility criteria. To be included, the articles had to meet specific population, intervention, comparison, and outcome criteria, such as results of a study having a population treated with venetoclax, results of a clinical trial or randomized clinical trial including venetoclax, or a review article on venetoclax. Additionally, all the selected articles were published in English, and we excluded studies that did not include venetoclax. The **Figure** illustrates the PRISMA flow diagram of the study selection.

Results

A total of 58 original articles about venetoclax were identified. The main focus of this article was to review venetoclax use in AML in different chemotherapeutic combinations. Chemotherapy drugs such as azacitidine and decitabine in combination with venetoclax show high safety profiles and are well tolerated in older patients with untreated AML. This combination is effective in high-risk groups such as patients 75 years or older, and, patients taking it have a lower incidence of gastrointestinal symptoms such as nausea, diarrhea, and low appetite.⁹

The phase 3 VIALE-A trial (NCT02993523) was designed to assess the effectiveness and safety of the azacitidine-venetoclax combination.¹⁰ Azacitidine at 75 mg/m² and venetoclax at 400 mg were given in combination daily from days 1 to 7 in patients with a new diagnosis of AML. According to the investigators, 433 patients, with a median age of 76 years and from 134 sites in 27 countries, were randomly assigned; 431 were included in the intention-to-treat population. Participants in the venetoclax/azacitidine group had a median overall survival of 14.7 months (95% CI, 12.1-18.7), whereas those in the azacitidine/placebo arm had a median survival of 9.6 (95% CI, 7.5-12.7) months. The HR for death was 0.66 (95% CI, 0.52-0.85; *P* < .001). Most notably, the combination produced quicker reactions than azacitidine only.¹¹

According to results from the study conducted by Kwag et al, decitabine in combination with venetoclax significantly improved the

FIGURE. PRISMA Flow Diagram of the Study Selection

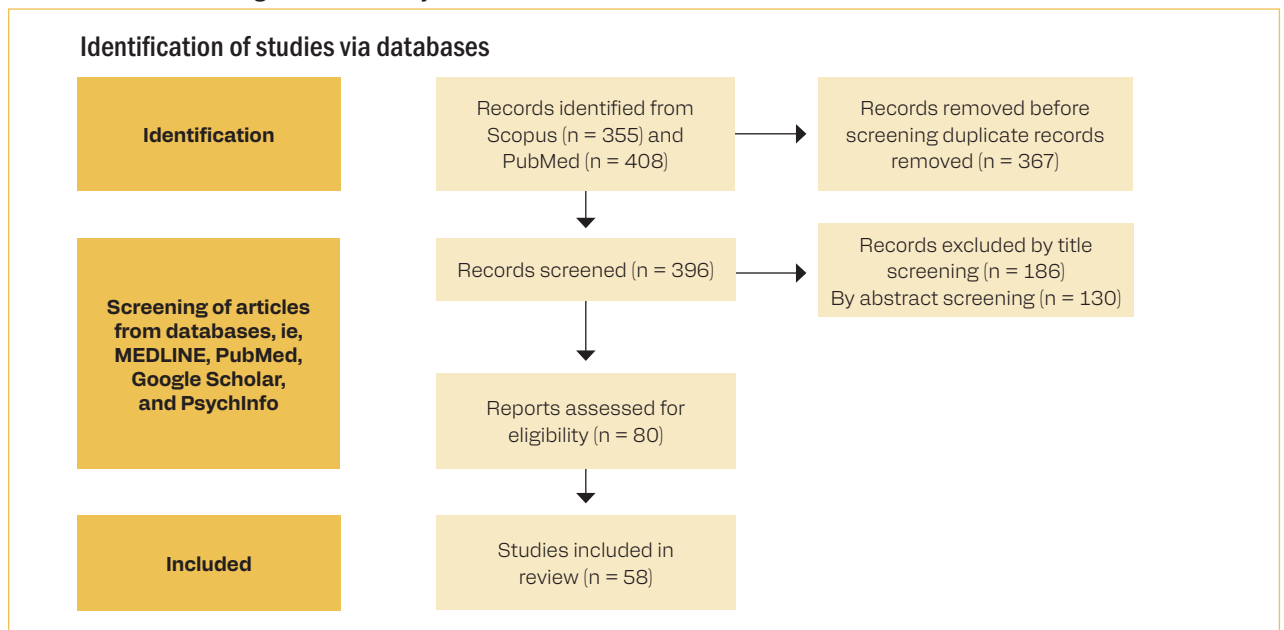


TABLE. Comparison of Therapeutic Agents

STUDIES	COMBINATION	RESULTS
Phase 3 VIALE-A (NCT02993523) ¹¹	Azacitidine plus venetoclax regimen	The venetoclax/azacitidine group had a median overall survival of 14.7 months.
Kwag et al ¹²	Decitabine plus venetoclax regimen	In older patients, the regimen significantly improved the response rates. Patients with AH SCT achieved leukemia-free status.
Bouligny et al ¹³	Decitabine plus venetoclax regimen comparison with azacitidine plus venetoclax	Measured tolerability, which showed universal cytopenias across all cell lines are not associated with venetoclax plus decitabine use.

AH SCT, allogeneic hematopoietic stem cell transplant.

response rates and survival outcomes in older patients with newly diagnosed AML compared with decitabine monotherapy. Additionally, 29% of patients who had allogeneic hematopoietic stem cell therapy (HSCT) achieved leukemia-free status with decitabine and venetoclax.¹²

According to Bouligny et al, participants in a retrospective study of decitabine plus venetoclax showed a more serious condition of thrombocytopenia compared with those taking azacitidine plus venetoclax, which depends on periods of transfusion. On the contrary, the degree of severe lymphocytopenia was lower in decitabine plus venetoclax.¹³

Patients with AML generally receive intensive chemotherapy as their primary treatment, which is far more dangerous and toxic, can lead to prolonged hospitalizations, and increases the risk for cardiologic and neurologic deficits. Alternatively, venetoclax with low-dose cytarabine is cost-effective, less toxic, and less hazardous to health than intensive chemotherapy.¹⁴ A comparison of different therapeutic combinations used in 3 studies is presented in the **Table**.

Discussion

Venetoclax and TP53-Mediated Apoptosis Pathway

Venetoclax is a selective B-cell lymphoma-2 (BCL2) inhibitor, an important protein in the TP53-mediated apoptosis pathway. It has been studied as monotherapy and combined therapy with other agents and has proven its effectiveness.¹⁵ BCL2 proteins play an important role in apoptosis and cell death through the intrinsic mitochondrial apoptotic pathway. Venetoclax produces its effect by binding to the BH3 domain of the BCL2 protein. This interaction leads to the production of proapoptotic proteins, which then leads to cell death. In AML, many cells express BCL2, and hence the use of venetoclax can lead to the death of many leukemic cells, playing an important role in AML therapy because cancer cells have increased survival and abnormal apoptotic processes.¹⁶

Venetoclax and Drug Resistance

Venetoclax is a groundbreaking cancer treatment that operates by targeting the BCL2 protein, inducing apoptosis (programmed cell death) in cancerous cells. The BCL2 protein plays a crucial role in regulating apoptosis, determining whether a cell survives or undergoes programmed death.¹⁷ Venetoclax, although promising, does not provide a cure for certain types of cancer such as AML or CLL. Furthermore, despite initial positive responses, prolonged exposure often leads to drug resistance, a complex phenomenon not yet fully elucidated.¹⁷⁻¹⁹

Molecular Factors Influencing Response to Venetoclax-Based Treatment

Genetic alterations and mutations constitute the key molecular factors that can also influence response to venetoclax-based treatment. Some mutations lead to increased positive response, whereas others lead to increased resistance to venetoclax. The use of venetoclax for a longer duration can cause upregulation of antiapoptotic proteins such as BCL-XL and MCL-1, leading to resistance. *IDH* and *NPM1* mutations are associated with increased rates of positive response, whereas mutations in *TP53*, *RAS*, and *FLT3* lead to resistance to venetoclax and venetoclax-containing regimens. Using venetoclax together with HMAs can improve the response rate to 93% in patients with *NPM1* and/or *IDH* mutations and also lead to improved rates of relapse-free survival.²⁰

Furthermore, patients with *TP53* mutations did not have favorable outcomes with venetoclax-based treatments, but those in other adverse-risk molecular subgroups showed improved clinical outcomes with certain venetoclax-based treatments. These include individuals with signaling mutations such as *PTPN11*, *RAS*, *FLT3-internal tandem duplication*, and *FLT3-tyrosine kinase domain*, and splicing mutations such as *ZRSR2*, *SF3B1*, *U2AF1*, and *SRSF2*.²¹ A small retrospective study by Nanaa et al

that enrolled patients with AML and myelodysplastic syndrome with *DDX41* mutations also indicated favorable responses to venetoclax combined with HMAs. Further research is needed to determine whether these mutations can serve as biomarkers for predicting venetoclax sensitivity. Molecular factors that influence response to venetoclax can be due to karyotype, specific mutations, and/or resistance mechanisms. A patient's karyotype, which may be adverse, intermediate, or favorable, affects how their leukemia responds to venetoclax. Studies comparing combination regimens in high-risk cytogenetic acute leukemia subsets with venetoclax vs those without venetoclax showed better remission rates, although overall survival remained the same in older and younger age groups.²²

Current evidence suggests that there are no dependable laboratory markers available to precisely predict sensitivity or resistance to venetoclax treatment. Venetoclax sensitivity appears to be influenced by various factors, including patient-specific variables, AML subtype, and specific gene mutations. Predicting responsiveness to venetoclax remains challenging.

Role of Venetoclax in AML After HSCT

Relapse after HSCT often occurs within 6 months, partly due to the longer period it takes the graft-vs-leukemia effect to develop to protect against AML relapse.²³ Most clinical trials aim to administer treatment within 2 to 3 months of transplantation. According to Schroeder et al, there are 2 types of post-HSCT maintenance therapy: prophylactic and preemptive treatments.²⁴ Several options can be considered for post-HSCT maintenance, such as FLT3 inhibitors, which are categorized into first-generation or multitarget agents including sorafenib (Nexavar), midostaurin (Rydapt), and sunitinib (Sutent). Those that are selective are also known as second-generation FLT3 inhibitors: quizartinib (Vanflyta), gilteritinib (Xospata), and crenolanib.²⁵

Venetoclax BCL2 inhibitors have recently been under investigation for their potential for use as maintenance therapy in a post-HSCT setting. An ongoing clinical trial is studying the efficacy of venetoclax combined with azacitidine. Moreover, a retrospective trial conducted by Amit et al studied venetoclax monotherapy in one group and donor lymphocyte infusions at increasing doses in another group. Both groups showed early signs of relapse with median survival of 6.1 months.²⁶⁻²⁸

Role of Venetoclax After HMA Failure

Hypomethylating monotherapy targeting AML is generally reserved for patients who are less able to tolerate the more intensive chemotherapy regimens, specifically the antileukemic chemotherapy regimen. HMA provides a much safer option for populations that are medically unfit or older.

However, due to its modest complete remission rates, this regimen is subject to failure. HMA failure is broadly divided into 2 categories. Primary failure is when the HMA regimen fails the patient (ie, the patient is in complete remission or complete remission but has an incomplete count recovery). Secondary failure refers to when a patient has an incomplete remission and an incomplete count recovery.^{28,29} In the subset of the AML population, the older regimen constituted a combination of LDAC, HMA, or some form of supportive care. The regimen was found to have fewer adverse effects in the older population. However, despite the safety profile, the complete response rates were not satisfactory, with a median survival of only 1 year.^{10,29}

A review article done by Aldoss et al illustrates the potential of venetoclax to be used off-label for patients with AML in whom HMA failed. Twenty-three patients in a prospective cohort were followed up, and a complete response rate of 43% was noted along with a median survival of less than 1 year after the addition of venetoclax to their HMA regimen.³⁰

Moreover, according to a retrospective study done by Tenold et al, patients with relapsed/refractory AML were divided into 2 groups. One received HMA monotherapy, and the second group received venetoclax plus HMA regimen. The venetoclax plus HMA group showed improved median overall survival and lower adverse effects compared with the HMA-only group. However, due to the lack of a definitive phase 3 trial and a limited number of patients, these findings are yet to be further investigated.³¹

Conclusion

This review article has included 58 original articles that emphasized the importance of the use of venetoclax in AML. This new emerging drug, when used in combination with other drugs, has transformed the treatment dynamic of acute myeloid leukemia. Venetoclax is a key treatment for AML with minimal adverse effects and can be used across all age groups. Physicians should prioritize the use of venetoclax along with combination drugs to prevent this deadly disease. We aim to bring attention to this promising aspect of venetoclax in the medical literature world. ■

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