Venetoclax in Combination with Hypomethylating Agents for the Treatment of Treatment-Naive B/Myeloid Mixed-Phenotype Acute Leukemia and Relapsed/Refractory Acute Myeloid Leukemia: A Report of 3 Cases

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Keywords
Venetoclax · Hypomethylating agents · Mixed-phenotype acute leukemia · Acute myeloid leukemia · Relapsed/refractory acute myeloid leukemia

Abstract
B/myeloid mixed-phenotype acute leukemia (MPAL) is an uncommon and aggressive leukemia without well-established treatment guidelines and has an inferior outcome. Relapsed/refractory (R/R) acute myeloid leukemia (AML) that is ineligible for aggressive chemotherapy regimens and allogeneic hematopoietic stem-cell transplantation has an extremely poor prognosis. The novel regimen of venetoclax (VEN) combined with hypomethylating agents (HMAs) has a synergistic therapeutic effect and a tolerable safety profile, which has been officially approved by the US Food and Drug Administration (FDA) for newly diagnosed AML in adults who are 75 years or older or patients precluding intensive induction chemotherapy. For R/R and other rare types of AML, no consensus has been reached on the efficacy of VEN-HMA. In addition, there is no available report on treatment-naive B/myeloid MPAL with VEN-HMA. Herein, we present 3 cases of VEN-HMA in treatment-naive B/myeloid MPAL and R/R AML. Its potential efficacy is worthy of further exploration in future researches.

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Introduction
Mixed-phenotype acute leukemia (MPAL) is an uncommon and aggressive leukemia without well-established standard treatment guidelines and has an inferior outcome [1]. However, acute myeloid leukemia (AML) is the most common type of acute leukemia diagnosed in adults and accounts for the largest number of deaths cause by leukemia [1, 2]. For MPAL, retrospective studies suggest better remission rates for ALL-like therapy as opposed to AML-like therapy [3]. For AML, relapsed/refractory (R/R) AML has poor prognosis. Physicians face considerable challenges in choosing the most favorable therapies, despite the numerous available ones, including aggressive chemotherapy regimens, allogeneic hematopoietic stem-cell transplantation.
(allo-HSCT), hypomethylating agents (HMAs), and molecular-targeted therapy, among others.

B-cell leukemia/lymphoma-2 (BCL-2, an antiapoptotic protein) inhibitors are regarded as the most promising targeted therapy drug for AML [4]. Venetoclax (VEN) is an oral, selective, small-molecule inhibitor of BCL-2. Studies have demonstrated that VEN in combination with HMA (VEN-HMA) has a promising synergistic therapeutic effect and a tolerable safety profile on untreated or R/R AML [5]. VEN-HMA or VEN plus low-dose cytarabine was officially approved by the US Food and Drug Administration (FDA) in October 16, 2020 for newly diagnosed AML in adults who are 75 years or older or patients with comorbidities precluding intensive induction chemotherapy. Herein, we present 3 patients who received the novel VEN-HMA therapy in our center. All the 3 patients signed the therapy-informed consent form; the study was based on the Declaration of Helsinki. Among them, one had treatment-naive B/myeloid MPAL, the other had R/R AML, and the last one had AML transformed from chronic myelomonocytic leukemia (CMML). To our knowledge, this is the first reported successful application case of VEN-HMA for treatment-naive young B/myeloid MPAL.

**Case Presentation**

**Case 1**

A 24-year-old male manifested with repeated fever and was found to have cytopenia with a low white blood cell of 0.60 × 10⁹/L, hemoglobin level of 83 g/L, and platelet of 26 × 10⁹/L on June 27, 2019. Bone marrow (BM) morphology showed that blast cells accounted for 73.5%; BM immunophenotyping showed that myeloid blasts accounted for 64.31% (CD117+/CD14+/CD13+), and B-lineage blasts accounted for 3.39% (CD19+/CD79a+/CD20+/CD22+); karyotyping analysis revealed 46,XY,+1,der(1;17)(q10;q10)[18]/46,XY[2]; next-generation sequencing showed PTPN11 and KMT2C gene mutations. Altogether, the patient was diagnosed with B/myeloid MPAL. However, the patient’s basic condition was poor because of the persistent high fever and severe pulmonary infection. Considering that the patient was not suitable for intensive induction chemotherapy, VEN + azacitidine therapy was introduced. The specific chemotherapy regimens of VEN-HMA treatment are shown in Table 1. This patient finally achieved complete hematological and molecular remission. A consolidated auto-HSCT treatment was subsequently performed on December 14, 2019. The follow-up was regular, and the patient showed complete remission (CR) >1 year later.

**Case 2**

A 41-year-old female presented with fatigue and was found to have an elevated white blood cell of 64.48 × 10⁹/L, hemoglobin of 110 g/L, and platelet of 62 × 10⁹/L on June 27, 2019. Bone marrow (BM) morphology showed that blast cells accounted for 82.5%; BM immunophenotyping showed that myeloid blasts accounted for 70.74% (CD117+/CD14+/CD13+), and B-lineage blasts accounted for 3.39% (CD19+/CD79a+/CD20+/CD22+); karyotyping analysis revealed 46,XY,+1,der(1;17)(q10;q10)[18]/46,XY[2]; next-generation sequencing showed PTPN11 and KMT2C gene mutations. Altogether, the patient was diagnosed with B/myeloid MPAL. However, the patient’s basic condition was poor because of the persistent high fever and severe pulmonary infection. Considering that the patient was not suitable for intensive induction chemotherapy, VEN + azacitidine therapy was introduced. The specific chemotherapy regimens of VEN-HMA treatment are shown in Table 1. This patient finally achieved complete hematological and molecular remission. All his characteristics before and after VEN + azacitidine treatment are shown in Table 1. No serious adverse reactions occurred during the treatment period, and the overall tolerance was well. A consolidative auto-HSCT treatment was subsequently performed on December 14, 2019. The follow-up was regular, and the patient showed complete remission (CR) >1 year later.
56 g/L, and platelet count of 89 × 10^9/L in January 4, 2019. BM morphology showed that monoblasts accounted for 82.5%; BM immunophenotyping revealed that monocyes accounted for 70.74%; next-generation sequencing showed NPM1, KRAS, and DNMT3A gene mutations. Altogether, the patient was diagnosed with acute monocytic leukemia (AML-M5). First, the patient was treated using standard induction chemotherapy with a 1 cycle regimen of cytarabine + idarubicin and achieved CR. Subsequently, the patient received an intensive regimen of mid-dose cytarabine + idarubicin + decitabine, mid-dose cytarabine + decitabine, and cytarabine + decitabine + etoposide in order. However, after the fourth chemotherapy cycle, BM examination suggested the recurrence of the disease. Unfortunately, she failed to achieve CR despite having received the fifth cycle regimen of decitabine + cytarabine + homoharringtonine + arubicin. Her BM morphology again showed that myeloblasts accounted for 67%. Because of her nonresponsive outcome as well as poor prognosis, VEN was added in the sixth cycle of chemotherapy combined with decitabine + pirarubicin + etoposide + cytarabine + thalidomide. The VEN + decitabine administration regimens are shown in Table 1. On the 14th day of treatment, the patient manifested with neutrophil deficiency, lung infection, and oral soft-tissue infection; the patient’s VEN dosage was decreased to 200 mg per day, which was maintained to the 21st day. After the chemotherapy of additional VEN, the next BM morphology showed that blast cells accounted for 8%; minimal residual disease showed that no myeloid blast exists. All her characteristics are shown in Table 1. Her prognosis was extremely poor even after receiving salvage allo-HSCT. Finally, the patient renounced the treatment and was discharged, and no follow-up was conducted.

Case 3
A 43-year-old male diagnosed with CMML for 2 years was admitted to our hospital in September 18, 2019 because he had progressed to AML transformed from CMML after 8 cycles of decitabine chemotherapy. BM morphology showed that myeloblasts accounted for 72.0%; BM immunophenotyping showed that myeloid blasts accounted for 67.29% 

Discussion
MPAL accounts for <5% of acute leukemias, including both biphenotypic leukemia (a leukemia with >1 lineage-defining marker on a single blast population) and bilineal leukemia (a leukemia composed of 2 or more single-lineage leukemia populations) [6]. Retrospective studies have shown an inferior outcome for MPAL than that for AML and ALL patients, with a median overall survival (OS) of 15–18 months [3]. AML is a highly heterogeneous malignant clonal hematologic malignancy in clinical performance and cytogenetics, which is characterized by the clonal expansion of myeloid blasts in the peripheral blood, BM, and/or other tissues [7, 8]. The average 5-year OS of AML is about 26% and that of R/R AML is about 5%–10% [7, 8]. CMML is a clonal disease of BM hematopoietic stem cells with dual features of myeloproliferative tumors and myelodysplastic syndrome. However, there is a high risk of rapid progression to AML within a short period of time, and the treatment of AML transformed from CMML is extremely difficult, and its mortality is very high. Although allo-HSCT is considered as the major curative approach for R/R AML, it is limited by numerous factors, including patients’ performance, donor source, treatment funding, and serious transplant-related complications. Patients with no access to allo-HSCT have an extremely poor prognosis and urgently require new effective treatment strategies.

VEN can inhibit the expression of BCL-2 protein family, which regulates the mitochondrial apoptosis pathway and participates in the occurrence, development, metastasis, and drug resistance of tumor cells [4]. Through the inhibition of DNA methyltransferase-1, HMA can cause DNA demethylation and cell differentiation or apoptosis to treat hematological malignancies [9]. Decitabine and azacitidine are considered as major HMA that have been recommended as low-intensity regimens for patients ineligible for intensive chemotherapy [9]. VEN-HMA is a novel, promising, and well-tolerated combination therapy for AML. DiNardo et al. [10] indicated that the OS was longer and the incidence of remission was higher among patients who received VEN + azacitidine than among those who received azacitidine alone in previously untreated AML who were ineligible for intensive chemotherapy. The median OS was 14.7 months, and the CR + CRi (CR with incomplete blood count recovery) was 66.4% in the VEN + azacitidine group [10]. In addition, DiNardo et al. [11] also reported a 61% CR + CRi of VEN-HMA in untreated elderly patients not eligible for standard induction therapy. Subsequently, they reported 68% CR + CRi, 11.3 months duration of CR + CRi, and 17.5 months median OS in an expansion study of VEN-HMA, and 400 mg daily was determined to have an optimal benefit-risk ratio compared with 800 mg or 1,200 mg daily. Subgroup efficacy analysis showed that patients with poor and intermediate risk cytogenetics had 60% and 74% CR + CRi, respectively [12]. For R/R AML, a phase II study (n = 32) showed that 19% of patients achieved a modest CR + CRi after VEN monotherapy 800 mg daily [13]. Another piece
of evidence from “real world” presented a 52% CR + CRi and 12% morphological leukemia-free state in 33 R/R AML patients treated with VEN-HMA [14]. Additionally, a case of T/myeloid MPAL relapsed after allo-HSCT was successfully treated with VEN + decitabine [15]. The above piece of literature indicates that VEN-HMA has a synergistic therapeutic effect, with a promising and broad application prospect in AML treatment both in the frontline and R/R settings. Generally, it is recommended that decitabine (20 mg/m^2 for 5 days) and azacytidine (75 mg/m^2 for 7 days) should be administered simultaneously with a starting dose of VEN 400 mg daily on the same day. The initial cycle duration of VEN is 28 days, and VEN dosage may need modification for cytopenia [5]. In summary, VEN-HMA is a novel and promising combination for patients ineligible for intensive chemotherapy or R/R AML. Further investigations should be conducted to evaluate VEN-HMA for management of R/R AML.

Generally, the clinical application of VEN-HMA is well tolerated, and the toxicities are manageable. Tumor lysis syndrome (TLS) is the most serious adverse event (AE) [5]. The risk of TLS can be effectively reduced by slowly increasing doses, conducting TLS risk stratification assessment, and closely monitoring TLS-related laboratory indicators [16]. Other common AEs include febrile neutropenia, anemia, thrombocytopenia, and lung infections. DiNardo et al. [12] reported that gastrointestinal and hematological AEs are the most common toxicities, and no TLS was observed. None of the 3 reported patients had serious life-threatening AEs related to VEN-HMA.

**Conclusion**

The novel VEN-HMA therapy demonstrates a promising efficacy and tolerable safety in treatment-naive and R/R AML. Besides, there is no available literature on treatment-naive B/myeloid MPAL with VEN-HMA. The actual and desirable efficacy of VEN-HMA should be further explored.

**Statement of Ethics**

For case 1, his written informed consent to publish this case report was obtained from the patient himself; for case 2 and case 3, their written informed consent for publication of this case report was obtained from their next of kin. The study was approved by the Institutional Review Board of the Wuhan Union Hospital (S113) in China and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Na Wang contributed to data collection, writing, and editing; Jing He contributed to data collection and revision; and Fang Liu contributed to data collection and revision.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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