Treatment of central nervous system relapse in PLZF::RARA-positive acute promyelocytic leukemia by venetoclax combined with arubicin and cytarabine: a case report

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Case Report

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Abstract

**Background:** Patients with refractory acute promyelocytic leukemia and central nervous system relapse often have a poor prognosis. Among them, patients with the *PLZF*: *RARA* rearrangement have a poor response to all-trans retinoic acid and conventional chemotherapy. Venetoclax, a selective inhibitor of B-cell lymphoma-2 (BCL-2), can cross the blood–brain barrier and has been widely used in the treatment of acute myeloid leukemia in recent years.

**Case presentation:** We report a case of central nervous system relapse in a patient with acute promyelocytic leukemia with *PLZF*: *RARA* rearrangement who achieved complete remission after treatment with anthracycline cytotoxic chemotherapy in combination with venetoclax. The concentration of venetoclax in the cerebrospinal fluid (CSF) was found to be approximately 1/1000 of that in the plasma based on liquid chromatography–tandem mass spectrometry. After the first treatment course, the *PLZF*: *RARA* test result for the patient’s marrow fluid sample turned negative. After the third treatment course, abnormal promyelocytic leukemia cells in the CSF were not detected using flow cytometry, and the *PLZF*: *RARA* test in the CSF remained negative.

**Conclusion:** This case report highlights a new approach to the treatment of central nervous system relapse in patients with *PLZF*: *RARA*-positive acute promyelocytic leukemia.

Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML). Translocation t(15;17) (q21;q22) is a cytogenetic abnormality that can be found in 95% of APL cases, which fuses the retinoic acid receptor alpha (*RARA*) and promyelocytic leukemia (*PML*) genes (*PML*: *RARA*) [1]. These patients often achieve complete remission (CR) following treatment with the all-trans retinoic acid (ATRA) arsenic trioxide (ATO) [2, 3]. However, some patients with APL carry variant chromosomal aberrations, in which the fusion of *RARA* with the promyelocyte leukemia zinc finger (*PLZF*) gene is the most common variant [4]. Patients with *PLZF*: *RARA*-positive APL respond poorly to ATRA. Their prognosis is worse than that of patients with *PML*: *RARA*-positive APL, making treatment relatively difficult [5]. Therefore, if a central nervous system (CNS) relapse occurs in such patients, treatment options are often limited and usually consist of conventional chemotherapy in combination with intrathecal chemotherapy (IT) [6]. Venetoclax has been reported to be effective in treating CNS relapses in patients with *PML*: *RARA*-positive APL [7]. However, to our knowledge, treatments for CNS relapse in *PLZF*: *RARA*-positive APL cases have not been reported to date.

Here, we report a case of CNS relapse in a patient with *PLZF*: *RARA*-positive APL in whom clearance of *PLZF*: *RARA* in the cerebrospinal fluid (CSF) was achieved after treatment with venetoclax, arubicin, and cytarabine.

Case Report
A 57-year-old female was admitted to our hospital with a “diagnosis of APL for more than 7 years and relapse in the CNS for more than 2 months.” The patient had no relevant family or social history. More than 7 years ago, the patient visited Shanghai Changzheng Hospital for anemia and was diagnosed with PLZF::RARA-positive APL after completing relevant examinations. After treatment with mitoxantrone and cytarabine (Ara-C) she achieved complete remission. Subsequently, she received consolidation and maintenance chemotherapy with mitoxantrone, pirarubicin, and etoposide, and received multiple intrathecal injections of methotrexate (MTX) and dexamethasone (Dex). During this period, the patient had been in CR. More than 2 years ago, the patient presented to our hospital with ecchymosis on both lower limbs and was diagnosed with APL relapse after completing the relevant examinations. The patient achieved CR<sub>MRD</sub>- (CR without measurable residual disease) of the APL relapse after treatment with idarubicin and Ara-C. Afterward, she received consolidation and maintenance chemotherapy with Ara-C, homoharringtonine, pirarubicin, and etoposide. Notably, the PLZF::RARA test remained negative. Just over 2 months ago, the patient visited our hospital again for bone marrow puncture, which showed that the PLZF::RARA test changed from negative to positive. At that time, the patient was admitted to our hospital with relapsed APL.

In the complete blood count, the white blood cell count was 3,700/mL, hemoglobin was 122 g/L, and platelet count was 272,000/mL. The coagulation profile, serum biochemical tests, stool routine, urinalysis, and tumor marker tests were all unremarkable. Bone marrow smear revealed that primitive cells and promyelocytes accounted for 3.5% of the nucleated cell count. PLZF::RARA tested positive in a bone marrow sample (qualitative testing) (Figure 1-a1). In bone marrow immunophenotyping, no abnormal myeloid cells and no abnormal phenotypic promyelocytes were detected. The patient was treated with venetoclax orally (100 mg D1, 200 mg D2, and 400 mg D3-21) in combination with arubicin (20 mg D1-4) and Ara-C (10 mg/m<sup>2</sup> q12h D1-14), starting on January 10, 2023. After treatment with venetoclax plus cytarabine, arubicin, and granulocyte colony-stimulating factor (V-CAG regimen), the PLZF::RARA test, performed from the bone marrow sample, turned negative (Figure 1-a2).

The patient was subsequently treated with the V-CAG regimen again, initiated on February 9, 2023. Venetoclax oral treatment was administered at a dose of 400 mg once a day. The patient subsequently underwent a lumbar puncture on February 13, 2023, with a CSF pressure of 200 mm H<sub>2</sub>O and 67 nucleated cells/mL (normal reference value: <8/mL). The CSF was positive for PLZF::RARA (3,599 copies, PLZF::RARA/ABL ratio 1.540) (Figure 1-b1). CSF flow cytometry showed that abnormal promyelocytic leukemia cells accounted for approximately 98.20% of the leukocytes (Figure 2). The patient was therefore diagnosed with relapsed and refractory PLZF::RARA-positive APL with CNS infiltration. After recovery from myelosuppression, the patient was administered a daily dose of 300 mg venetoclax for 7 days in combination with intermediate-dose Ara-C (1000 mg/m<sup>2</sup> q12h D1-3), from March 17, 2023, onward.

During this period, the patient received nine intrathecal injections of MTX and Dex. We conducted liquid chromatography–tandem mass spectrometry (LC-MS/MS) of CSF and plasma specimens on February 18, 2023, and March 21, 2023. We confirmed the presence of venetoclax in the CSF, which was
approximately 1/1000 of the peak plasma concentration (Figure 3). The number of nucleated cells and proportion of abnormal promyelocytic leukemia cells in the patient's CSF gradually decreased (Figure 4). Finally, on March 24, 2023, abnormal promyelocytic leukemia cells were no longer detected in the patient's CSF using flow cytometry. The PLZF::RARA test, from a CSF sample, changed from positive to negative (Figure 1-b2). At the time of writing, the patient is awaiting for hematopoietic stem cell transplantation.

Discussion

Most patients with APL carry PML::RARA, but few patients carry rare fusion genes of RARA, including PLZF, NPM1, NUMA1, STAT5B, PRKAR1A, FIP1L1, BCOR, and TBLR. One rare form is PLZF::RARA-positive APL, which is characterized by insensitivity to arsenic and retinoic acid [8]. Extramedullary relapse of PLZF::RARA-positive APL is a rare phenomenon associated with a poor prognosis.

The CNS is the most common site of extramedullary relapse, for which no recognized effective treatment exists [9]. Venetoclax, a highly selective BCL-2 inhibitor, has recently been shown to cross the blood–brain barrier [10]. To date, there have been no reports of CNS relapse in patients with PLZF::RARA-positive APL treated with venetoclax.

Our patient received V-CAG as a first course, and the PLZF::RARA test in the bone marrow fluid sample turned negative. At the beginning of the second course, APL relapse in the CNS was found during IT chemotherapy, and the V-CAG regimen was administered again. The third course involved intermediate-dose Ara-C combined with venetoclax. During this period, nine IT injections of Dex and MTX were administered. We found a gradual decrease in the number of nucleated cells in the CSF. Moreover, CSF flow cytometry testing showed that the proportion of abnormal promyelocytes in the CSF also gradually decreased. Finally, the PLZF::RARA test in the CSF changed from positive to negative. This rare type of APL responded to venetoclax.

Zhang et al. demonstrated that venetoclax with IT injection support resulted in remission in patients with PML::RARA-positive APL showing CNS relapse [7]. Li et al. showed that patients with PML::RARA-positive APL who were treated with venetoclax and azacitidine after a negative response to chemotherapy achieved CR [11]. Venetoclax is effective for patients with chronic lymphocytic leukemia involving the CNS [10, 12]. Our case of PLZF::RARA-positive APL with CNS relapse achieved CR after receiving V-CAG in combination with IT injections. This indicated that venetoclax combined with CAG is a potential solution for patients with specific types of APL.

It is also worth examining whether venetoclax can enter the CSF and whether its concentration changes in the CSF. Studies have shown that venetoclax can be detected in the CSF and that its concentration is approximately 1/300th to 1/1000th of that in the plasma [7, 10]. In our case, we first confirmed the presence of venetoclax in the CSF during the second course of treatment, during which venetoclax was administered at a dose of 400 mg/day. In the third course of treatment, we measured the concentration of venetoclax and found that the peak concentration in the plasma was 2,760 ng/mL, whereas the
concentration in the CSF was 2.01 ng/mL. Therefore, we believe that during the course of subsequent treatment, the concentration of venetoclax in the CSF would reach an effective concentration. Therefore, venetoclax has a good therapeutic effect on patients with APL involving the CNS.

Interestingly, in the literature, we found several descriptions of APL cases with rare fusion genes that were treated with venetoclax. The positive fusion genes in these cases included STAT5B::RARA, HNRNPC::RARA, and THRAP3::RARA [13–15]. These special types of APL cases, with no CNS involvement, have also achieved good results.

In summary, our case study demonstrated that venetoclax combined with CAG might be a good treatment option for certain patients with APL with CNS involvement. However, establishing the efficacy of venetoclax in CNS involvement in patients with APL will require evidence from larger-scale, prospective, randomized trials.

**Abbreviations**

Acute promyelocytic leukemia (APL), acute myeloid leukemia (AML), retinoic acid receptor alpha (RARA), promyelocytic leukemia (PML), complete remission (CR), all-trans retinoic acid (ATRA), arsenic trioxide (ATO), central nervous system (CNS), intrathecal chemotherapy (IT), cerebrospinal fluid (CSF), methotrexate (MTX), dexamethasone (Dex).

**Declarations**

**Ethics approval and informed consent**

This study involving human participants was reviewed by Zhoushan Hospital Ethics Committee. Informed consent was obtained from the patient for the treatment.

**Availability of data and materials**

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

**Competing interests and funding**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This work was supported by the Zhou Shan Public Welfare Foundation, China, under grant number 2019c31101. The funder had no other role in the study.

**Author contributions**
ZZ and HX designed the study. ZZ wrote the original manuscript. FZ and HX reviewed and edited the manuscript. ZZ collected and analyzed the data. HX collected cerebrospinal fluid. HW and FL collected the data. All authors contributed to the article and approved the submitted version.

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**References**


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Figures
Figure 1

PLZF::RARA test result in bone marrow sample and cerebrospinal fluid (CSF) by fluorescence RT-PCR.  
(a1) PLZF::RARA before the first V-CAG regimen treatment on December 12, 2022 (qualitative examination).  
(a2) PLZF::RARA test result in bone marrow sample after the first V-CAG regimen treatment on February 6, 2023 (qualitative examination).  
(b1) PLZF::RARA test result in CSF on February 13, 2023 (quantitative examination).  
(b2) PLZF::RARA test result in CSF on April 9, 2023 (quantitative examination)

Figure 2

Cerebrospinal fluid (CSF) flow cytometry: In the CSF sample, a total of 10,876 effective cells were collected. Abnormal cell population: blasts accounted for 98.20% of nucleated cells, mainly expressing CD33; partially expressing CD56, CD117, and CD11c; and weakly expressing CD13
Figure 3

Venetoclax plasma and cerebrospinal fluid (CSF) levels by liquid chromatography–tandem mass spectrometry (LC-MS/MS). (a) In the second course, the presence of venetoclax was first confirmed in the CSF on February 18, 2023, with a concentration of 3.88 ng/ml. (b) Plasma venetoclax peak concentration was approximately 2,760 ng/ml on March 21, 2023. (c) Venetoclax concentration in the CSF was approximately 2.01 ng/ml on March 21, 2023.
Figure 4

Trends in nucleated cell counts and acute promyelocytic leukemia cell counts in the cerebrospinal fluid