Case Report

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

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Abstract

Objectives: Patients suffering from refractory acute promyelocytic leukemia with central nervous system relapse often have a poor prognosis. Among these patients, those with *PLZF::RARA* rearrangement exhibit poor responses to all-trans retinoic acid and conventional chemotherapy. Venetoclax, a selective inhibitor of B-cell lymphoma-2, can cross the blood–brain barrier and has been widely applied to acute myeloid leukemia therapy recently.

Case presentation: A case of central nervous system relapse in a patient with acute promyelocytic leukemia harboring *PLZF::RARA* rearrangement was successfully treated with anthracycline cytotoxic chemotherapy and cytarabine in combination with venetoclax, resulting in complete remission. Liquid chromatography-tandem mass spectrometry revealed that the concentration of venetoclax in the cerebrospinal fluid (CSF) was approximately 1/1,000 of that in plasma. Following the first treatment course, the patient's bone marrow sample tested negative for *PLZF::RARA*. 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.

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

Keywords: acute promyelocytic leukemia; *PLZF::RARA*; central nervous system; relapse; venetoclax; case report

Introduction

Acute promyelocytic leukemia (APL) is one subtype of acute myeloid leukemia. Translocation t(15;17) (q22;q21) or (q24;q21) 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) with all-trans retinoic acid and arsenic trioxide therapy [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 all-trans retinoic acid, whose prognosis remains more serious relative to that of patients with *PML*::*RARA*-positive APL, posing a challenge in treatment [5]. Therefore, if a central nervous system (CNS) relapse occurs among such patients, treatment options are often limited and usually consist of conventional chemotherapy in combination with intrathecal (IT) chemotherapy [6]. Venetoclax is efficient for treating CNS relapses in patients suffering from *PML::RARA*-positive APL [7]. However, no cases of treatment have been reported for CNS relapse in patients with *PLZF::RARA*-positive APL.

Here, we report a case of CNS relapse in a patient with *PLZF::RARA*-positive APL in whom clearance of *PLZF::RARA* in CSF was achieved following therapy by venetoclax, arubicin, and cytarabine (Ara-C). This study has been approved by the Ethics Committee of Zhoushan Hospital-Nr.:2023/308. We have obtained the patient's written informed consent.

Case report

A 57-year-old woman with no relevant family or social history was admitted to the hospital with a diagnosis of APL for over seven years and CNS relapse for over two months. In December 2015, the patient presented to Zhoushan Hospital with anemia and was diagnosed with *PLZF::RARA*-positive

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APL after undergoing relevant examinations. The patient's risk score placed the patient in the low-risk category. After treatment with mitoxantrone and Ara-C, the patient achieved CR. Subsequently, she underwent consolidation and maintenance chemotherapy with mitoxantrone, pirarubicin, and etoposide, along with multiple intrathecal (IT) injections of methotrexate (MTX) and dexamethasone (Dex). Throughout this period, the patient had been in CR. In June 2020, 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 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 was negative. In December 2022, the patient revisited Zhoushan Hospital for a bone marrow puncture, which showed that the *PLZF::RARA* test changed from negative to positive. At that time, she was admitted to the hospital suffering from relapsed APL.

Complete blood count revealed a white blood cell count of 3,700/mL, hemoglobin level of 122 g/L, and platelet count of 272,000/mL. Coagulation profile, serum biochemical tests, stool routine, urinalysis, and tumor marker tests all remained within normal limits. Bone marrow smear examination showed that primitive cells and promyelocytes comprised 3.5 % of the nucleated cell count. *PLZF::RARA* testing from a bone marrow bone marrow sample yielded a positive result (qualitative testing) (Figure 1-a1). Bone marrow immunophenotyping did not detect any abnormal myeloid cells or abnormal phenotypic promyelocytes.

The patient commenced treatment on January 10, 2023, receiving venetoclax orally (100 mg day 1, 200 mg day 2, and 400 mg days 3–21) in combination with arubicin (20 mg days 1–4) and Ara-C (10 mg/m^2 every 12 h, days 1–14). After treatment with venetoclax plus Ara-C, arubicin, and granulocyte colony-stimulating factor (V-CAG regimen), the *PLZF::RARA* test conducted on a bone marrow sample yielded a negative result (Figure 1-a2).

The patient underwent a second course of the V-CAG regimen, starting on February 9, 2023. Venetoclax was orally administered at a dosage of 400 mg per day. On February 13, 2023, a lumbar puncture was performed, with a CSF pressure of 200 mm H_2O and 67 nucleated cells/mL. The CSF was

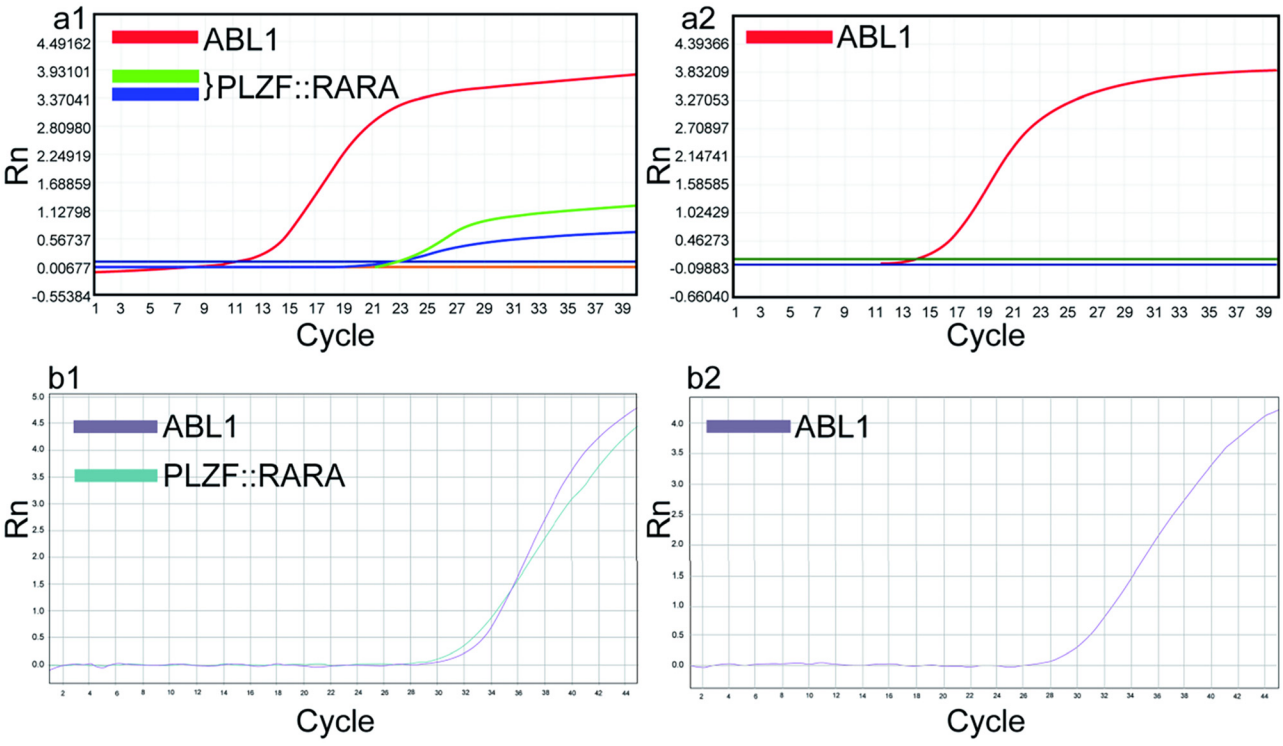

Figure 1: *PLZF::RARA* test result in bone marrow sample and cerebrospinal fluid (CSF) by fluorescence RT-PCR. (a1) *PLZF::RARA* before the first V-CAG regimen treatment on December 12, 2022 (qualitative examination). (a2) *PLZF::RARA* test result in bone marrow sample after the first V-CAG regimen treatment 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)

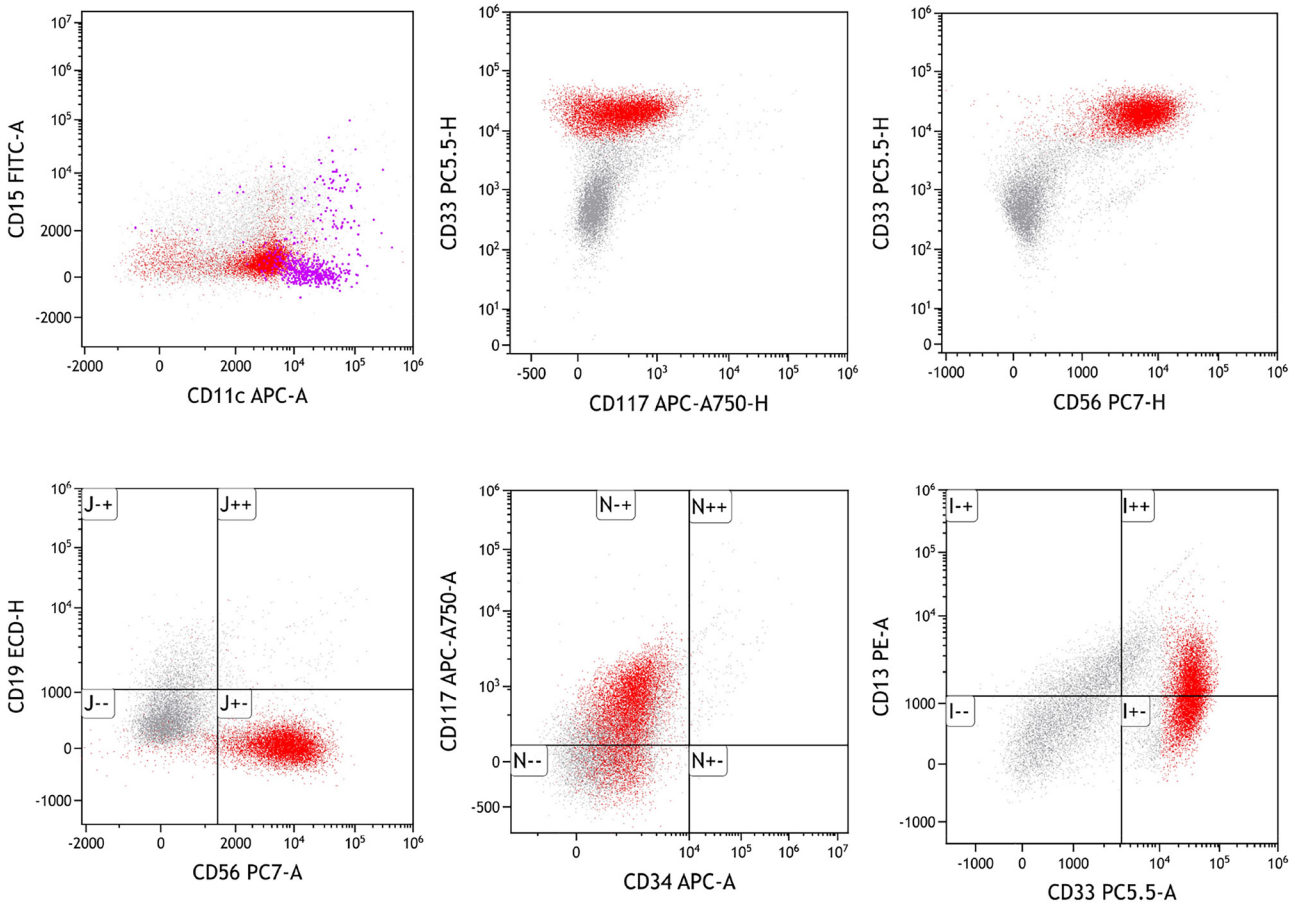

Figure 2: Cerebrospinal fluid (CSF) flow cytometry. In the CSF sample, 10,876 effective cells were collected on February 13, 2023. Abnormal cell population: blasts accounted for 98.20 % of nucleated cells, mainly expressing CD33, partially expressing CD56, CD117, and CD11c, and weakly expressing CD13.

positive for *PLZF::RARA* (3,599 copies, *PLZF::RARA/ABL* ratio 1.540) (Figure 1-b1). Flow cytometry analysis of the CSF revealed that abnormal promyelocytic leukemia cells accounted for approximately 98.20 % of the leukocytes (Figure 2). Consequently, the patient was 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 seven days in combination with intermediate-dose Ara-C (1,000 mg/m^2 every 12 h, days 1–3) from March 17, 2023, onward.

During this period, the patient underwent nine intrathecal injections of MTX and Dex. Liquid chromatography-tandem mass spectrometry of CSF and plasma specimens was performed on February 18, 2023, and March 21, 2023. Venetoclax was detected in the CSF at approximately 1/1,000 of the peak plasma concentration (Figure 3). The number of nucleated cells and the 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 by flow cytometry. The *PLZF::RARA* test from a CSF sample was now negative (Figure 1-b2). As of today, the patient is awaiting allogeneic hematopoietic stem cell transplantation (Allo-SCT).

Discussion

Most patients with APL carry *PML::RARA*; however, few patients carry rare fusions of *RARA* with other genes, including *PLZF*, *NPM1*, *NUMA1*, *STAT5B*, *PRKAR1A*, *FIP1L1*, *BCOR*, and *TBLR*. One rare form is *PLZF::RARA*-positive APL, which is resistant to arsenic and retinoic acid [8]. Extramedullary relapse of *PLZF::RARA*-positive APL is uncommon and associated with a poor prognosis.

The CNS is a common site of extramedullary relapse and has no standard effective treatment currently [9]. Venetoclax, a highly selective B-cell lymphoma-2 inhibitor, has recently been found to cross the blood–brain barrier [10]. To date, CNS relapse in patients with *PLZF::RARA*-positive APL treated with venetoclax has not been reported.

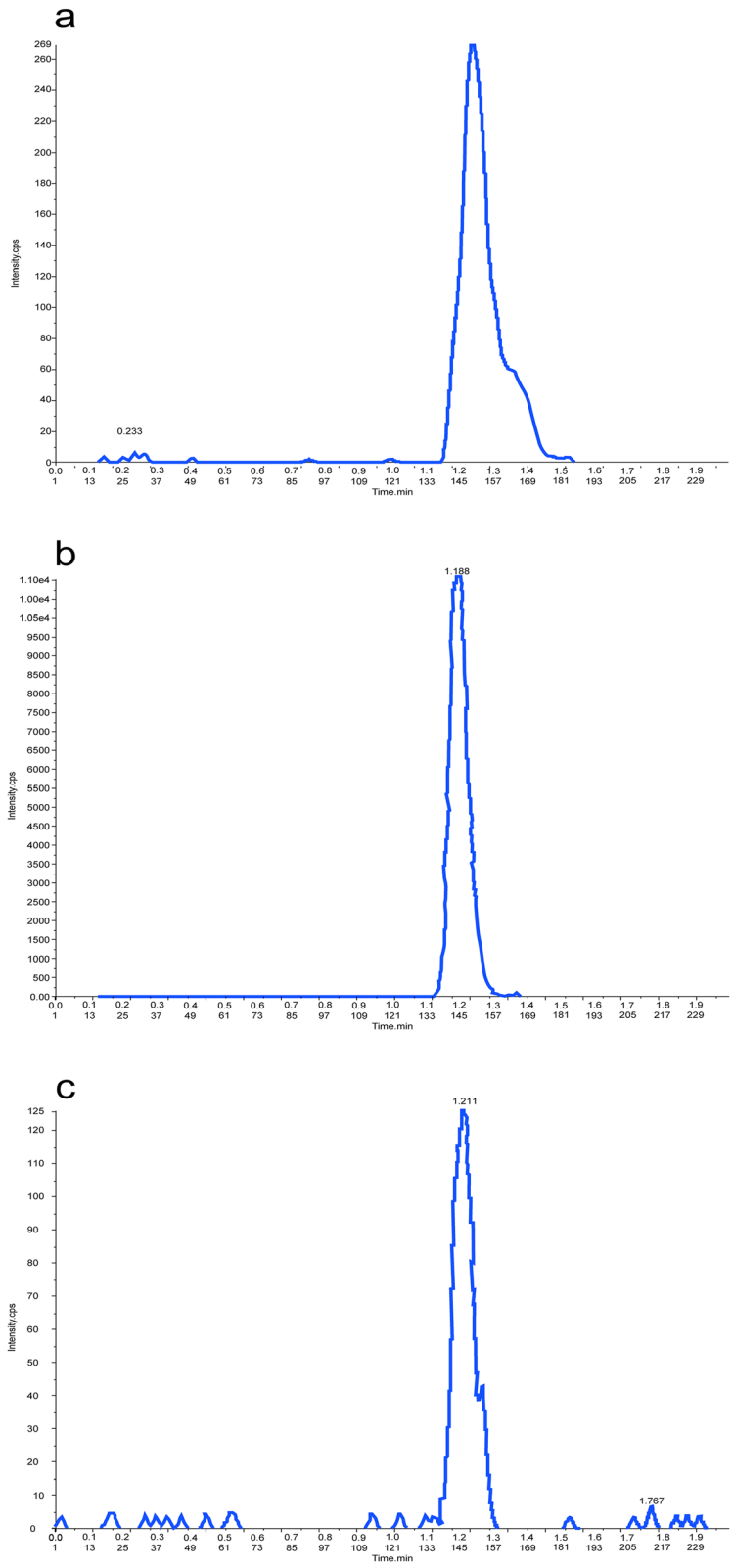

Figure 3: Venetoclax plasma and cerebrospinal fluid (CSF) levels by liquid chromatography-tandem mass spectrometry. (a) In the second course, the presence of venetoclax was first confirmed in the CSF on February 18, 2023, with a concentration of 3.88 ng/mL. (b) Plasma venetoclax peak concentration was 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.

Our patient received V-CAG as initial therapy, and the *PLZF::RARA* test in the bone marrow fluid sample was negative. However, during intrathecal (IT) chemotherapy at the beginning of the second course, APL relapse in the CNS was detected and the V-CAG regimen was administered again. The third course consisted of intermediate-dose Ara-C

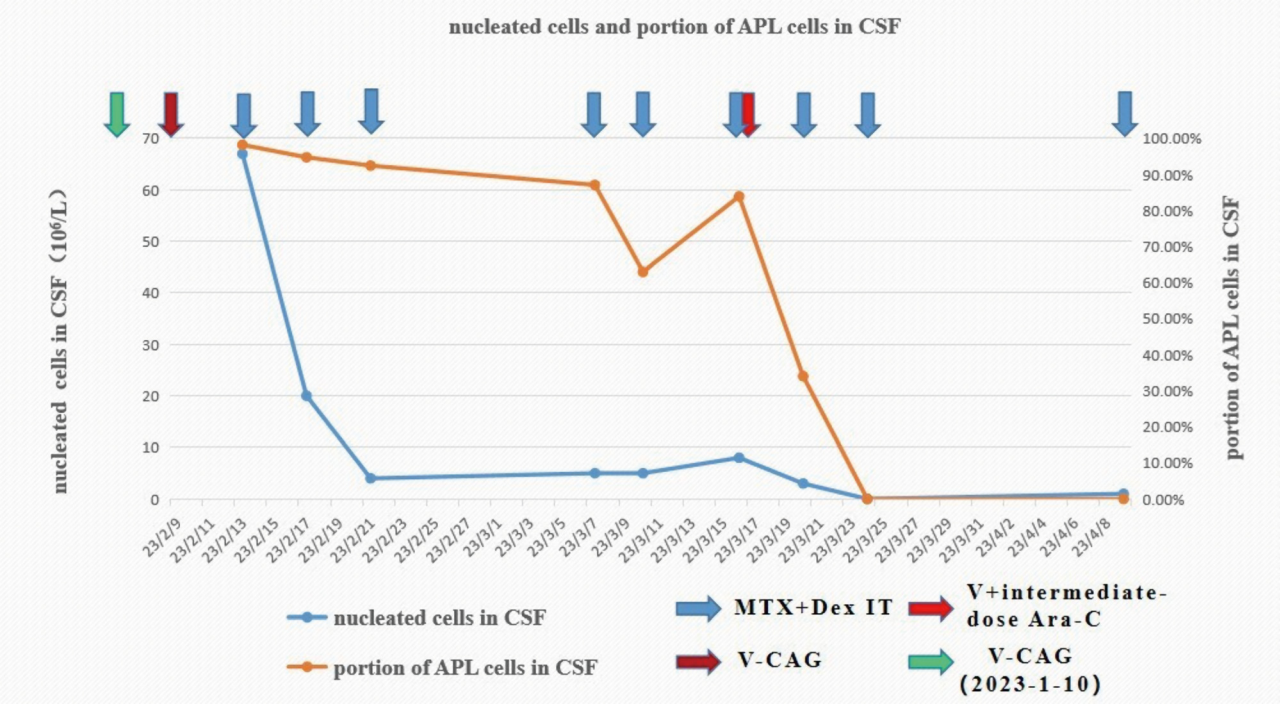

Figure 4: Trends in nucleated cell counts and acute promyelocytic leukemia cell counts in the cerebrospinal fluid.

combined with venetoclax. During this period, nine IT injections of Dex and MTX were administered. A gradual decrease in the number of nucleated cells in the CSF was observed. Moreover, CSF flow cytometry revealed a gradual decrease in the proportion of abnormal promyelocytes in the CSF. Finally, the *PLZF::RARA* test in the CSF was negative, indicating that this rare type of APL responded to venetoclax. For the upcoming allo-SCT, we intend to use a conditioning regimen consisting of granulocyte colony-stimulating factor (G-CSF), fludarabine (Flu), Ara-C, and idarubicin administered sequentially with Flu and busulfan. For patients with refractory leukemia, this regimen has demonstrated a 3-year overall survival of 43.8 % and an event-free survival of 42.3 % [11].

Zhang et al. [7] reported a case report that venetoclax with IT injection support resulted in remission in a patient with *PML::RARA*-positive APL showing CNS relapse. Li et al. [12] reported that a patient with *PML::RARA*-positive APL who was treated with venetoclax and azacitidine after a negative response to chemotherapy achieved CR. Venetoclax is efficient for patients suffering from chronic lymphocytic leukemia involving the CNS [10, 13]. Our case of *PLZF::RARA*-positive APL with CNS relapse achieved CR after receiving V-CAG in combination with IT injections. This finding suggests that venetoclax combined with CAG may be a promising therapeutic strategy for patients with specific types of APL.

It is worth examining whether venetoclax can penetrate the CSF and whether its concentration fluctuates within the CSF. Venetoclax can be detected in the CSF at concentrations approximately 1/300th to 1/1,000th 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, when 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 plasma concentration 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 will reach effective levels. Therefore, V-CAG combined with IT demonstrates promising therapeutic efficacy for patients with APL involving the CNS.

Recently, a study showed that compared to traditional cytoreduction therapy, pediatric APL treated with venetoclax cytoreduction is less likely to stop using retinoic acid and arsenic due to differentiation syndrome and is easier to achieve hematological CR. Children treated with venetoclax cytoreduction also exhibit reduced reliance on platelet and plasma infusions [14]. In our case, when APL relapses in the CNS, the proportion of abnormal promyelocytic leukemia cells in the CSF is very high. After V-CAG and IT treatment, the patient did not experience disseminated intravascular coagulation and only received a small amount of platelets

without plasma infusion, which is consistent with the results reported above.

In the literature, we found several descriptions of APL cases with rare fusion genes that were treated with venetoclax. The fusion genes detected in these cases included *STAT5B::RARA*, *HNRNPC::RARA*, and *THRAP3::RARA* [15–17]. Treatment of these special types of APL cases, with no CNS involvement, 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 potency of venetoclax in CNS involvement in patients with APL will require evidence from larger-scale, prospective, randomized trials.

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Research ethics: This study conforms to the principles of the Helsinki Declaration and has been approved by the Ethics Committee of Zhoushan Hospital (Ethics Committee of Zhoushan Hospital-Nr.:2023/308).

Informed consent: Informed consent was obtained from all individuals included in this 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.

Competing interests: Authors state no conflict of interest.

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Data availability: The data and materials that support the findings of this study are available on request from the corresponding author, HX, upon reasonable request.

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