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Oral etoposide combined with oral arsenic plus retinoic acid for two cases with newly diagnosed high-risk acute promyelocytic leukemia during COVID19 pandemic

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ABSTRACT

Acute promyelocytic leukemia (APL) is a highly curable hematology malignancy. The major factor influence prognosis of APL is early deaths (ED) during the course of induction therapy, especially in high-risk APL. Therefore, effective reduction of white blood cells and correction of coagulation abnormalities are the key points of treatment for high-risk APL. Due to COVID19 pandemic in China since Jan 2020, some patients with hematologic malignancies suspected of COVID-19 infection had been isolated and traditional intravenous chemotherapy drugs is not available in isolated wards. We had explored a regimen of an oral etoposide to reduce the tumor burden for high-risk APL and dual induction with retinoic acid (ATRA) and oral arsenic realgar-Indigo nautralis formula (RIF), and finally two cases of high-risk APL patients received complete remission in one month. It is indicated that pure oral induction regimen: oral etoposide, ATRA and RIF provides a novel therapy in outpatient clinics.

Acute promyelocytic leukemia (APL) is a highly curable hematology malignancy. The clinical characteristics are unique: 1. The onset of the disease is often accompanied by severe bleeding tendency and patients are prone to disseminated intravascular coagulation (DIC); 2. The typical feature of the APL cell and classic cytogenetics is t (15;17) (q22; q12) or typical molecular change are diagnostic criteria [1]. Retinoic acid (ATRA) and arsenic highly altered the prognosis of APL with the complete remission rate 90–94% or higher and diseases free survival (DFS) rate 80–90% or higher [2-4].

2019 ELN recommendations defined APL patients with a WBC count $\leq 10 \times 10^9$/L before induction as low risk and APL patients with a WBC count$>10 \times 10^9$/L as high risk, which definitely emphasize the critical role of initial WBC count on the prognosis [5]. ATRA plus ATO-based regimen with addition of some cytoreductive chemotherapy were used in high-risk APL patients, guidelines from ELN and NCCN recommended chemotherapy (idarubicin or daunorubicin alone or combined with cytarabine),or Gemtuzumab ozogamicin (GO) as cytoreductive therapy [5, 6]. 2018 Chinese guideline for APL recommended hydroxyurea (Hu), anthracyclines and cytarabine as cytoreductive therapy [7].

Despite ATRA and ATO highly altered the prognosis of APL, early deaths remain the major effect on cure rate of APL. Park et al. reported ED rate of APL in induction is 10–17.5% in [8], and a retrospective study in Brazil reported 43 out of 134 (32%) patients died during induction and the bleeding complications were the most frequent cause of early deaths, 26/43 (60.5%) [9]. Several studies demonstrated that leukocytosis is prone to coagulopathy (hemorrhagic death), DS and severe acute respiratory syndrome (ARDS) [10, 11]. Therefore, effective and safe reduction of WBC count is the key point to reduce the early mortality of high-risk APL. Single agent Hu is difficult to control the rapid multiplication of APL cells in high-risk patient, and oral anthracyclines were not available in China, so we try to use oral etoposide instead.

In December 2019, novel coronavirus pneumonia cases were reported in Wuhan, Hubei Province, World Health Organization (WHO) defined it as coronavirus disease 2019 (COVID-19). It rapidly spread, resulting in a global pandemic. [12]. COVID-19 viral RNA detection by PCR is specific diagnostic marker, however, the sensitivity of nasopharyngeal swab-PCR in COVID-19 patients is only nearly 30%, so negative results of PCR can't exclude COVID-19 infection. Strictly isolated suspected patients to certain area (febrile clinics or isolation wards in emergency rooms) prevented transmission in hospital [13]. Intravenous

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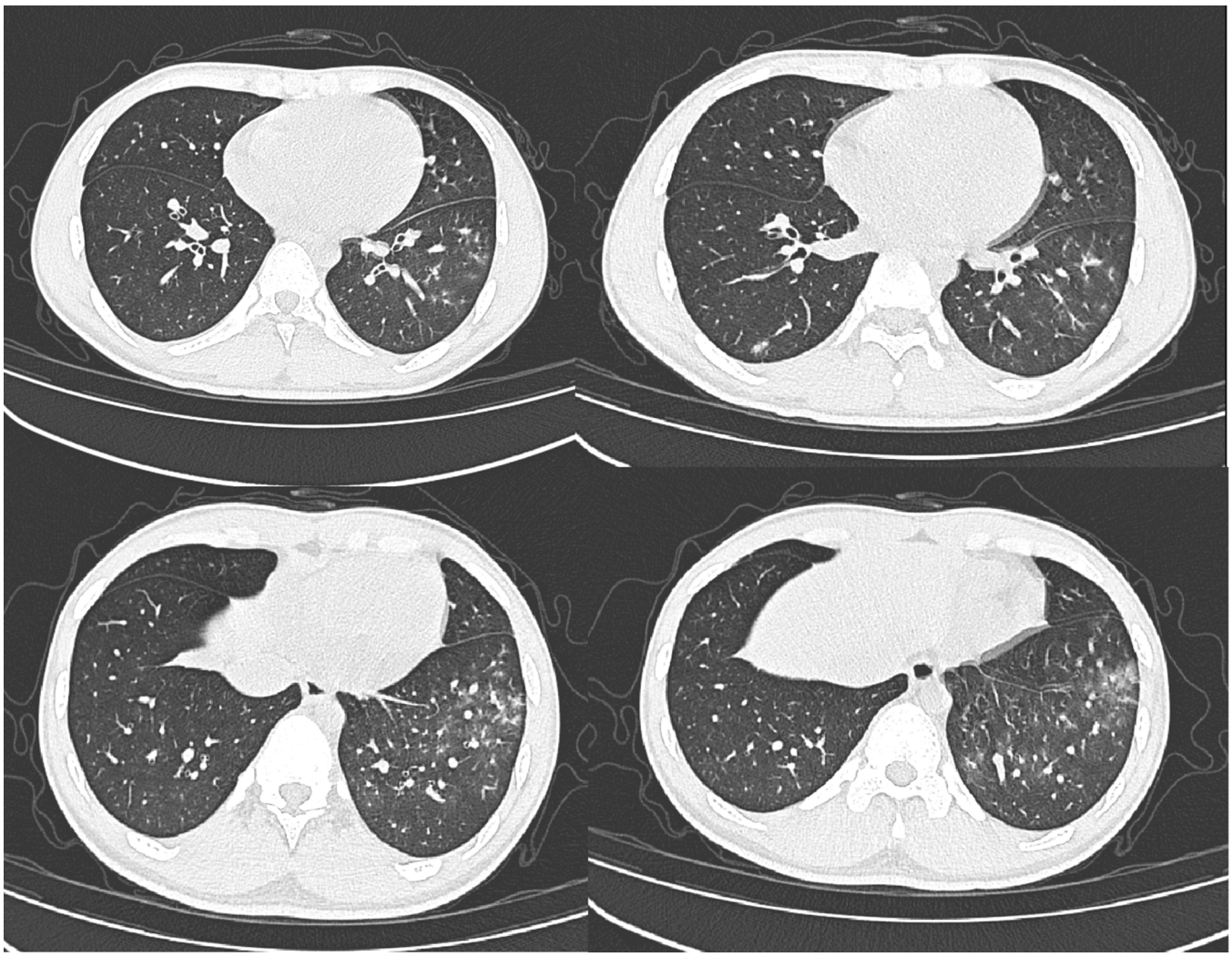


Fig. 1. Case 1 Chest CT 2020–1–31

chemotherapy was not available in isolation ward.

During COVID-19 pandemic, our center explored the regimen of oral etoposide as cytoreductive therapy combined with oral RIF plus ATRA based oral drug induction regimen for two high-risk APL patients, both of the patients reached complete remission in about one month.

1. Case 1

Patient No 02,048,211, male, 21 years old, 176 cm/67 kg, he went to the outpatient clinics due to intermittent fever for more than 2 months on Jan 30th 2020.

The patient had fever on Dec 1st, 2019, without chills or other symptoms, Tmax of 38.2 °C. He went to the local hospital and received some Chinese traditional medicine to relieve symptoms, from then on patient had intermittent low-grade fever. On January 30, 2020, patient suffered from gingival bleeding, he carried out some laboratory tests in the local hospital. CBC: WBC 28.63 $\times$ 10^9/L, Hb 94 g/L, PLT 7 $\times$ 10^9/L. Coagulation analysis: PT 15.5 s, Fib 120 mg/dL, d-dimer 2614 ng/ml. Chest CT showed infection in the upper and middle lobe of the right lung; localized atelectasis in the lingual segment of the left upper lobe and possible infection; and localized atelectasis in the lower lobe of the left lung (Fig. 1). The patient was controlled as a suspected case in the isolation ward according to fever, multiple pulmonary patchy shadows and a history of direct contact with relatives in Wuhan, although COVID-19 PCR of throat swab was negative three times.

On Feb 1st 2020, the patient had dry tap bone marrow aspiration, and peripheral blood (PB) smear showed typical APL. The patient was treated with ATRA, Hu, allopurinol and sodium bicarbonate for leukemia and with imipenem for anti-infection and with adequate supportive transfusion of red blood cells, platelets, fibrinogen and prothrombin complex. On Feb 2nd 2020, patient complained about headache and dizziness. No abnormality was found on brain CT scan. CBC: WBC 25.95 $\times$ 10^9/L, Hb 62 g/L, PLT 8 $\times$ 10^9/L, and leukostasis was suspected and oral Vp-16 100 mg Qd (Brand name: Lastet; Manufacturer: kabuskiki kaisha Japan Co., Ltd) was taken to reduce tumor burden and dexamethasone 5 mg QD preventing DS. On Feb 10th 2020 coagulopathy was corrected completely. On Feb 12th 2020 PML-RARA (Bcr1 isoform) in peripheral blood was 80.0%, so APL (high-risk) was diagnosed. RIF 60 mg/kg/d were administrated. During the course of induction, patient suffered from intermittent fever, pulmonary infection and acute orchiepididymitis, so imipenem, vancomycin, oseltamivir and voriconazole were administrated for anti- infection. We monitored the complete blood count trend (Fig. 3-1). Hepatic function: ALT 21–72 U/L, AST 23–49 U/L, TBIL 12.1–14.7umol/L. On February 25th, 2020, the chest CT examination showed that both lung lesions returned to normal. On Mar 3rd, 2020, CBC: WBC 2.28 $\times$ 10^9/L, Hb 75 g/L, PLT 88 $\times$ 10^9/L, and peripheral blood smear showed no APL cells. On Mar 3rd, 2020, bone marrow aspiration showed no promyelocytes, PML-RARA quantification in bone marrow 8%. Lumbar puncture and intrathecal injection were performed to prevent central nervous system leukemia, routine

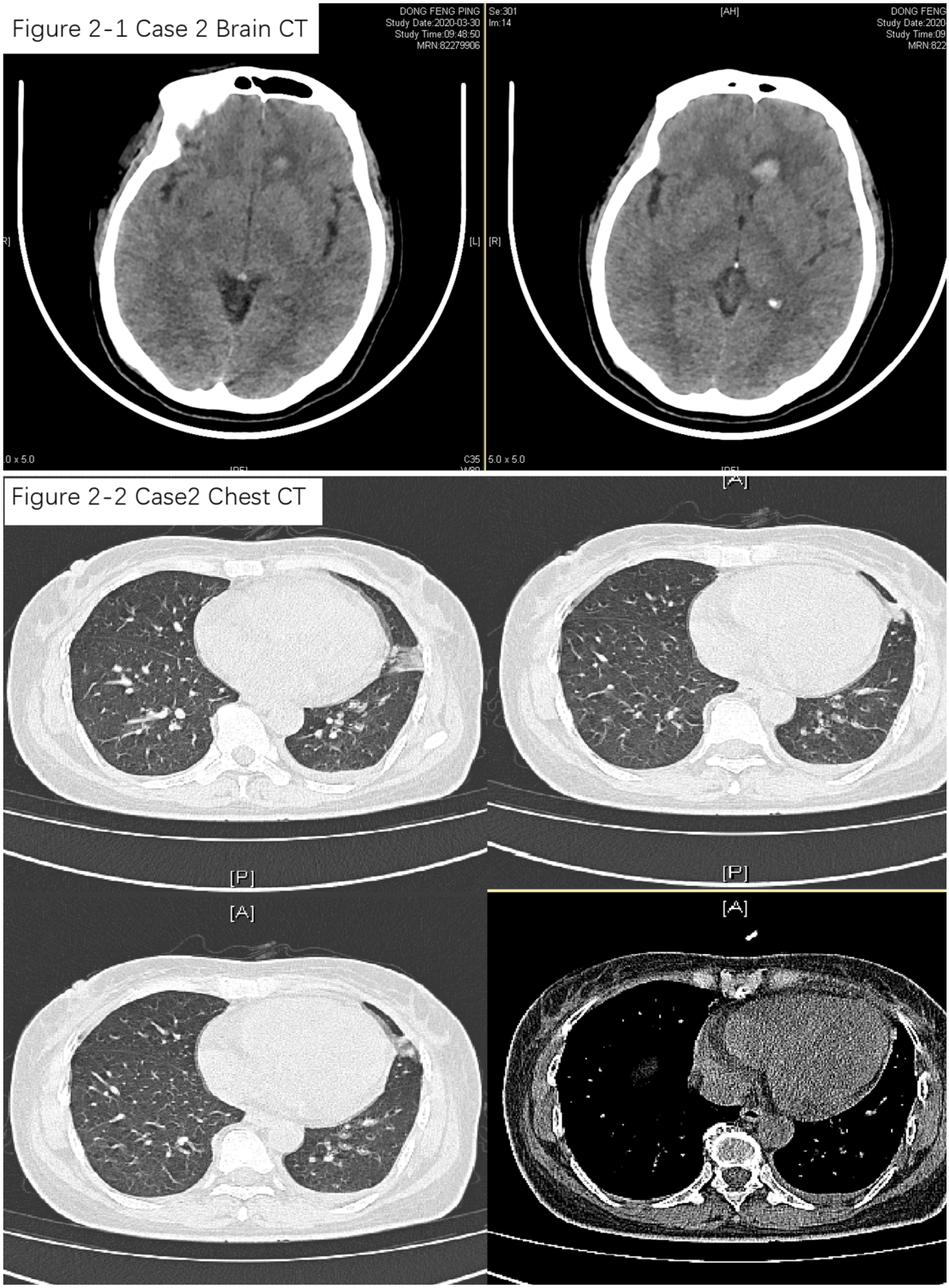
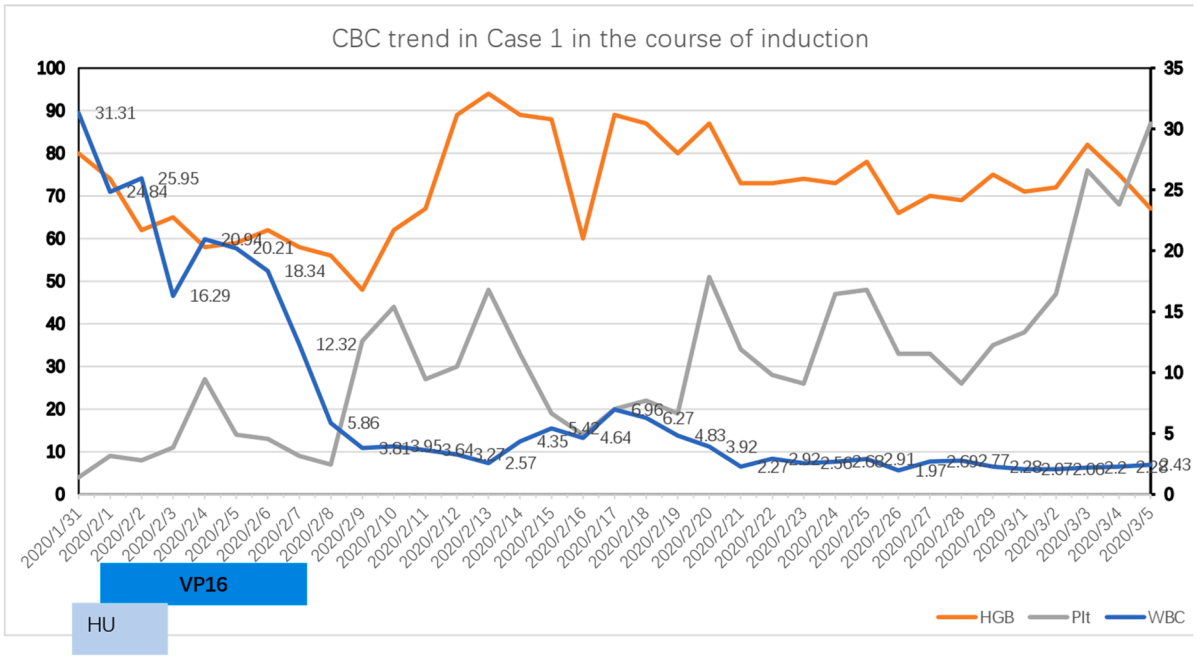
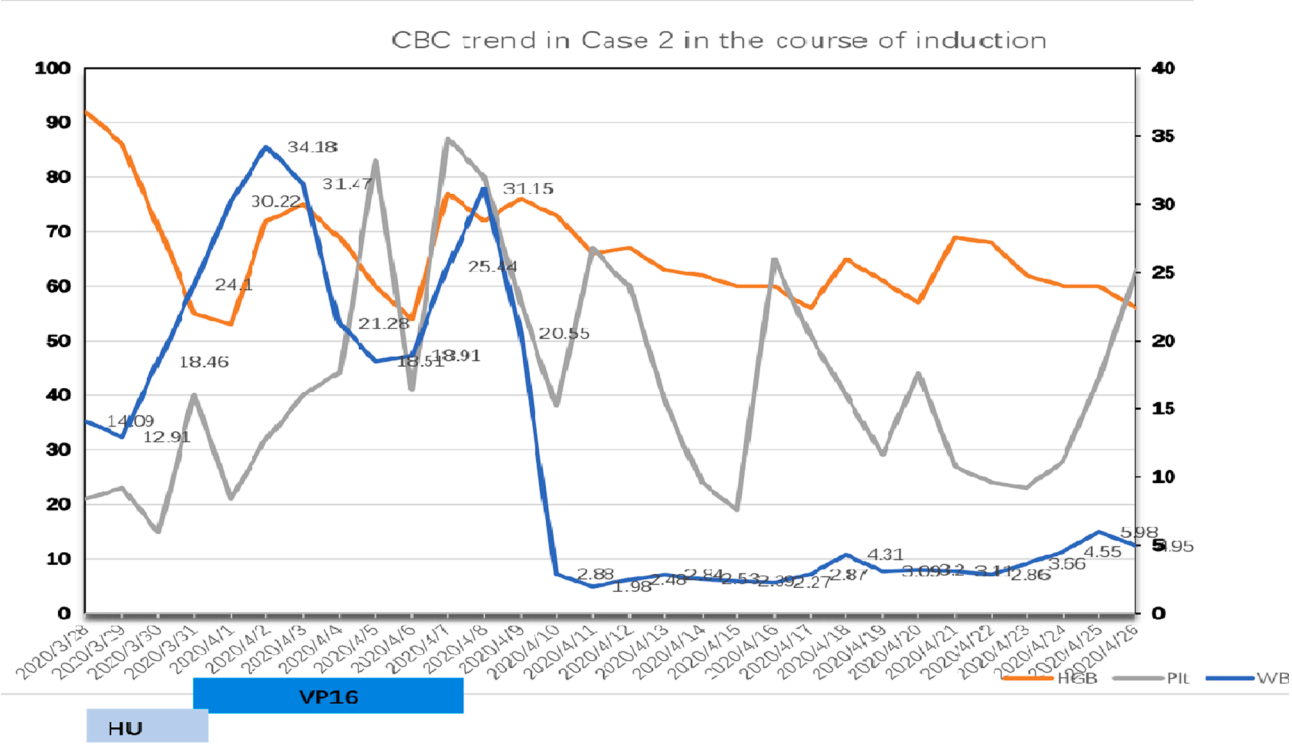


Fig. 2. Case 2 Brain CT 2020–3–28

biochemical test of cerebrospinal fluids showed no abnormality. The patient achieved hematological remission, and all other complications were cured. Case 1 patient was treated with VP16 750 mg and Hu 11 g in total, 35 days of ATRA (25 mg/m^2/d) and 28 days of RIF (60 mg/kg/d), then morphological evaluation of bone marrow showed complete remission. The patient only suffered from grade 1 hepatic dysfunction, no renal dysfunction and no QTc prolongation. The coagulopathy was corrected completely on the 8th day after ATRA. CBC returned to normal on 45 days since the initial treatment. 34 g fibrinogen, 10 U red blood cells and 17 U platelets were infused in total.



3-1 CBC trend in Case 1 in the course of induction



3-2 CBC trend in Case 2 in the course of induction

Fig. 3. CBC trend in the course of induction

2. Case 2

Patient No 02,048,387, female, 50 years old, 154 cm/65 kg, she went to the fever clinics due to ecchymosis for 2 weeks and headache for 1 day.

Multiple ecchymosis was found in her lower extremities since middle March 2020, however she did not go to the hospital for further examination. Then, the activity tolerance decreased gradually. On Mar 27th, 2020, a sudden onset with high fever (Tmax 39.1 °C) was observed, accompanied by headache, no disturbance of physical activity, no abnormal sensation and no disturbance of consciousness. She went to fever clinics in our hospital. CBC showed WBC 14.09 × 10^9/L, Hb 92 g/

L, PLT 15 × 10^9/L. Coagulation analysis: PT 19.7 s, Fib 90 mg/dL, d-dimer 38,102 ng/ml. Brain CT showed cerebral hemorrhage near the anterior horn of left lateral ventricle and ruptured into the anterior horn of adjacent lateral ventricle (acute stage). There were a few lacunar foci in bilateral basal ganglia (Fig. 2). Chest CT: new infection in the upper field of right lung and middle lobe of right lung; localized atelectasis in lingual segment of left upper lobe and possible infection; localized atelectasis in lower lobe of left lung. There was a small amount of pleural effusion and pericardial effusion on the left side. COVID-19 PCR of throat swab was negative twice. Meropenem was administrated for anti-infection, and mannitol was administrated for dehydration to reduce intracranial pressure, and adequate supportive transfusion of red blood cells, platelets, fibrinogen and prothrombin complex were infused to maintain hemostasis. The patient was isolated in fever clinics for treatment owing to high fever and new cerebral hemorrhage.

2020–3–29 The patient was diagnosed as APL. The morphology showed 96% hypergranular APL cells, and MPO is strong positive. FCM: 84.14% abnormal clonal myeloid cells which express CD33,CD117,CD9, CD64,CD13,CD123, and CD7,CD34,CD10,CD19,CD56,CD2,CD15 are all negative. PML-RARA (Bcr1 isoform) is positive 67.4% and Chromosome Analysis is t (15;17) (q24;q21) . ATRA 20mgQd~Bid and Hu 3–4 g/d was administrated for leukemia. 2020–3–31 WBC elevated to 24.1 × 10^9/L, and patient complained about headache, so oral Vp-16 was given to reduce tumor burden, and dexamethasone 5 mg QD preventing DS. Then, the temperature fell within normal range with no headache. We monitored the complete blood count trend (Fig. 3-2). On April 10th, 2020 coagulopathy was corrected completely, and RIF (60 mg/kg/d, divided into three times) were administrated. During the course of dual induction, patient suffered from intermittent fever, pulmonary infection, gingival abscess and Gram positive cocci sepsis (Staphylococcus enteromeningococci), and meropenem, piperacillin tazobactam and vancomycin were administrated for anti-infection. 2020–4–14,2020–4–24 PB smear showed no APL cells. On April 30th, 2020, bone marrow aspiration showed no promyelocytes, PML-RARA quantification in bone marrow 1.9%. Lumbar puncture and intrathecal injection were performed on 2020–4–25,2020–4–27 to prevent central nervous system leukemia, routine biochemical test of cerebrospinal fluids showed no abnormality. The patient was treated with VP16 650 mg and Hu 14 g in total, 33 days of ATRA (25 mg/m^2/d) and 28 days of RIF (60 mg/kg/d), then morphological evaluation of bone marrow showed complete remission. Maybe due to tendency of differentiation syndrome, bloodstream infections or intracerebral hemorrhage, or all of them, elevated white blood cell counts are difficult to control. In order to prevent fatal differentiation syndrome, ATRA was administrated less than 25 mg/m^2/d in the first 13th day and RIF was not administrated at beginning. The patient had no hepatic dysfunction, renal dysfunction and QTc prolongation. The coagulopathy was corrected completely on the 13th day after ATRA. CBC returned to normal on 33 days since the initial treatment. 45 g fibrinogen, 12,300 U prothrombin complex, 10 U red blood cells and 14 U platelets were infused in total. No obvious sequelae of central nervous system had been found until now.

3. Discussion

Our previous study demonstrated that ATRA plus RIF is not inferior to ATRA plus intravenous ATO in non-high-risk APL patients [14]. Therefore, we chose ATRA plus RIF regimen as basic therapeutic drugs for high-risk APL patients. Different from other types of acute leukemia, the major reason affecting the prognosis of APL is early mortality rather than relapse. ED usually occurs within 2–3 weeks of induction therapy. In particular, early deaths (ED) mostly due to the disease-associated coagulopathy, and hemorrhagic events account for 40–65% of ED, and the most common is cerebral hemorrhage and cerebral hemorrhage is the most common cause [10, 15]. High-risk APL patients are prone to hemorrhagic death, DS and leukostasis. Therefore, cytoreductive therapy can help reduce the incidence fatal complications of high-risk APL [5].

Etoposide (Vp-16) is a topoisomerase II inhibitor antitumor agent which is widely used in the treatment of several hematologic malignancies. Hydroxyurea is a nonalkylated antitumor drug, which can inhibit DNA synthesis. 2018 Chinese guideline recommended Hu as the first line cytoreductive agent when WBC>4 × 10^9/L during induction [7]. Single agent Hu is difficult to control the rapid multiplication of APL cells in high-risk patients according to our previous clinical experience. NCCN and ELN guidelines recommended anthracyclines or GO due to stronger cytoreductive effect. Lumbar puncture and IT chemotherapy is elective both in ELN guidelines and Chinese guidelines, however we usually do 2–4 times Lumbar puncture and IT chemotherapy in high-risk APL to prevent central nervous system leukemia (CNSL).

The successful experience of these two patients demonstrated that:1. Cytotoxic drug oral Vp-16 replace anthracyclines as cytoreductive agent at the initial stage of induction therapy for high-risk APL;2. Oral Vp-16 is convenient and it overcomes the limitation of intravenous chemotherapy drugs in some special circumstances; 3. High-risk APL patients should receive oral Vp-16 as early as possible to reduce tumor load in order to secure safety of induction therapy. 4. Oral regimen could avoid Peripherally Inserted Central Catheter, so it could avoid catheter venous thrombosis in the coagulopathy during the early stage. In conclusion, oral Vp-16 cytoreductive regimen combined with ATRA and RIF dual induction therapy is expected as a new mode of high-risk APL treating in outpatient clinics or emergency room, which is worth to explore in the future.

CRediT authorship contribution statement

Sheng-ye Lu: Writing – original draft, Writing – review & editing. **Li Wen-jing:** Project administration. **Rui Lou:** Project administration. **Rui Ma:** Project administration. **Ji-hong Zhu:** Project administration. **Hao Jiang:** Investigation, Project administration.

Declaration of Competing Interest

We declare no competing interests.

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