Clinical Case Report

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Acute myeloid leukemia in an 86-year-old man with AML1/ETO treated with Homoharringtonine and Arsenic Trioxide

A case report

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Abstract

Rationale: Acute myeloid leukemia (AML) is a malignantly clonal and highly heterogeneous disease. Although the treatment of AML has brought promising outcomes for younger patients, prognosis of the elderly remains dismal. Innovative regimens are increasingly necessary to be investigated.

Patient concerns: We present an 86-year-old AML patient with fever, cough, and sputum production.

Diagnoses: A diagnosis of AML with maturation (AML-M2) and AML1/ETO was made.

Interventions: The patient was treated with a regimen of Homoharringtonine coupled with arsenic trioxide.

Outcomes: The AML-M2 patient with AML1/ETO achieved incomplete remission, but showed few toxic side effects and improved survival. Besides, we analyzed the dynamic counts of complete blood cells during the treatment. The count of white blood cell had a positive correlation with the percentage of blast cells ($r=0.65$), both of which had a negative correlation with the percentage of segmented neutrophils ($r=-0.63, -0.89$).

Lessons: Homoharringtonine and arsenic trioxide may induce both the apoptosis and differentiation of leukemic cells in AML-M2 with AML1/ETO.

Abbreviations: AML = acute myeloid leukemia, AML-M2 = AML with maturation, As_2O_3 = Arsenic Trioxide, Hb = hemoglobin, HHT = Homoharringtonine, PLT = platelet, WBC = white blood cell.

Keywords: acute myeloid leukemia, AML1/ETO, Arsenic Trioxide, Homoharringtonine

1. Introduction

Acute myeloid leukemia (AML) is a malignantly clonal disorder characterized by blockage of differentiation in the myeloid lineage and an accumulation of its immature progenitors in bone marrow, leading to hematopoietic failure.[1] In China, it was predicted that there were about 75,300 newly diagnosed leukemia cases in 2015; meanwhile, it was estimated that about 53,400 Chinese died of leukemia in 2015.[2] Age has been recommended as one of the poorest prognostic indicators for overall survival over the past decades. Although the changing treatment schedules and transplantation have shown benefits in AML of younger patients, response to treatment and survival in older ones remains dismal.[3] Here, we reported a successful case of 86-year-old man with AML treated with traditional Chinese medicines (TCM), Homoharringtonine and Arsenic, showing few toxic side effects and improved survival.

2. Consent

This study was approved by Ethical Committee of Union Hospital Affiliated to Fujian Medical University (2018YF037-02), and written informed consent was obtained from the patient's family for publication of this case report and accompanying images.

3. Case presentation

An 86-year-old man with fever, cough and sputum production for 7 days, was admitted to our hospital in November 2016. The medical history revealed the patient diagnosed with malignant lymphoma by the biopsy of cervical lymph node 4 years ago, had received 6 courses of standard chemotherapy (CHOP regimen), and had 5 years history of diabetes. Apart from the signs of anemia in the aged man, peripheral blood counts revealed white

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blood cells (WBC) 40.05×10^9/L, segmented neutrophils 2%, hemoglobin (Hb) 76.0 g/L, platelet (PLT) 74.0×10^9/L, and blast cells accounted for 90% of nucleated cells. Bone marrow was examined in an effort to establish the diagnosis, showing a marked hypercellularity with 68% myeloblasts, the occurrence of Auer rods, and 100% positive myeloperoxidase staining. AML1-ETO fusion gene was also detected. Consequently, the elderly patient was diagnosed with AML-M2 based on French–American–British classification.

He was treated with Homoharringtonine 2 mg/d and arsenic trioxide (As_2O_3) 10 mg/d after the initial diagnosis. But Homoharringtonine and As_2O_3 were replaced by supportive therapy due to overt myelosuppression 4 days later. Peripheral blood examination revealed WBC 1.71×10^9/L (myeloblasts decreased to 25% and segmented neutrophils increased to 51% of all nucleated cells), Hb 44.0 g/L, and PLT 13.0×10^9/L. Surprisingly, no myeloblast was detected and segmented neutrophils were 34% at day 9 after the chemotherapy. Whereas the follow-up count of WBC increased to 73.43×10^9/L and myeloblasts increased to 97% at day 47 after his first chemotherapy. The initial regimen of Homoharringtonine and As_2O_3 were reused. The count of WBC returned to normal 3 days later and the chemotherapy was then discontinued. In order to reduce the degree of myelosuppression, we chose the regimen of As_2O_3 between 5 mg × 7 day and 10 mg × 7 day, alternately. Meanwhile, the regimen of Homoharringtonine between 0.5 mg × 7 day and 1 mg × 7 day was adopted, alternately. No myeloblast was detected in the peripheral blood cell smear with myelocytes 23%, metamyelocytes 22%, and segmented neutrophils 51% after 2 courses of the regimen above.

Analyzing the correlations among complete blood cell counts with Spearman test[4] in our case, we found some features as follows: The patient displayed an abnormally elevated count of WBC, and aberrantly decreased counts of PLT and Hb at his first visit, which was consistent with pathological feature of AML. Besides, the count of WBC had a positive correlation with the percentage of blast cells ($r = 0.65$), but a negative correlation with the percentage of segmented neutrophils ($r = -0.63$). The percentage of blast cells had a negative correlation with the percentage of segmented neutrophils ($r = -0.89$). It may be explained by the differentiation from blast cells to segmented neutrophils after chemotherapy. However, the counts of PLT and Hb had no correlation with the other parameters above (Fig. 1).

4. Discussion

Usually, AML patients have no evident causes. Exposure to chemotherapy is 1 risk factor associated with increased incidence with age. In our case, the patient with lymphoma had received chemotherapy for 6 cycles before the diagnosis of AML-M2, the cause of which may be the chemotherapy. In addition, AML1-ETO fusion gene was found in the case diagnosed with AML-M2. Whether the occurrence of AML1-ETO gene is before lymphoma or not, is not known. AML1-ETO gene is the product of t(8;21)(q22;q22) translocation in AML patients. AML1-ETO keeps the function of DNA binding sites in AML1 and the ability to recruit relevant cofactors through ETO, promoting granulopoiesis with inhibition of erythropoiesis in bone marrow.[5]

Older AML patients (age >60 years) have always been one of the most challenging group to treat. These patients have different tolerance of toxicity, and treatments are hardly curative. Treatment-related mortality of elderly patients with intensive treatment is more common (10%–40%) than that of younger patients (<10%).[1] Innovative chemotherapy regimens are thus necessary to be investigated. A randomized controlled, phase 3 trial study in 609 AML patients (14–59 years old) from China reported that the Homoharringtonine based HAA regimen (Homoharringtonine, aclarubicin, and cytarabine) had a higher complete remission (CR) rate and survival advantage than the daunorubicin and cytarabine regimen.[6] More recently, a retrospective research of 140 patients (16–60 years old) with t(8;21)AML revealed that the HAA regimen provided good molecular response and achieved much higher CR rate after 1 cycle of induction treatment, compared to other regimens reported in t(8;21)AML.[7] Thus, the Homoharringtonine based regimen may be a better choice in AML, especially in t (8; 21) AML. Arsenic, with a 500-year history in TCM, was successfully used to treat acute promyelocyte leukemia (APL) in TCM principle of counteracting one toxin with another.[8,9] In 2000, Chinese researchers reported that the CR rate and the 5-year survival rate of 136 APL patients treated with As_2O_3 were 87.9% and 92.0%, respectively.[10]

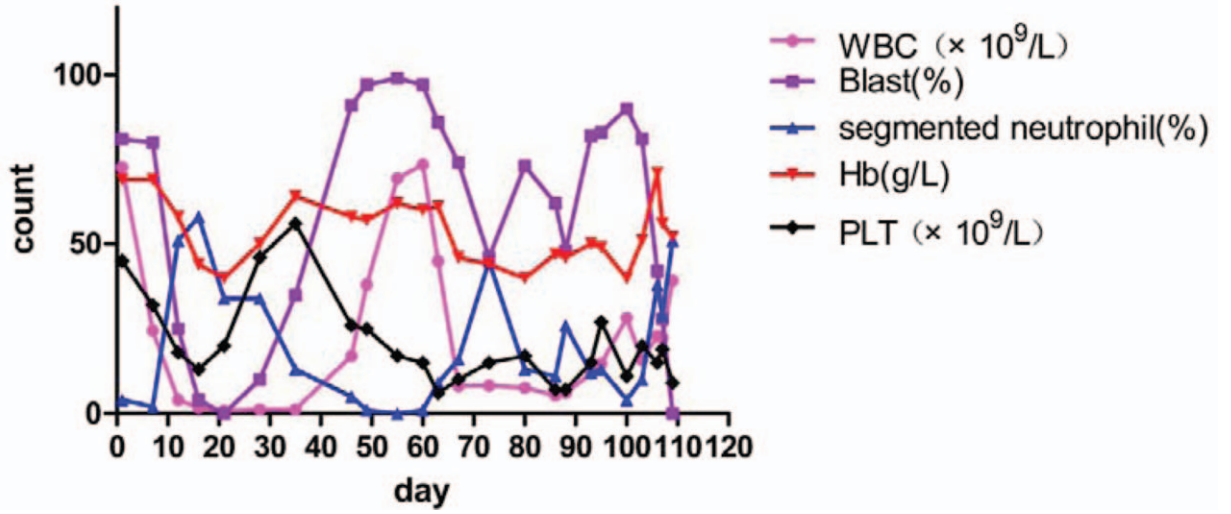

Figure 1. Count: the count of WBC ($4.0–10.0 \times 10^9$/L), Hb (120–160 g/L), PLT ($100–300 \times 10^9$/L), or percentages of Blast and segmented neutrophil; day: the time of peripheral blood examination from the first visit to the time of myeloblasts removed. Hb = haemoglobin, PLT = platelet, WBC = white blood cell.

On the basis of the encouraging results above, we selected Homoharringtonine coupled with As_2O_3 to treat the 86-year-old case diagnosed as AML-M2 with AML1-ETO fusion gene, and a good response was achieved after the 2-cycle chemotherapy. We observed leukocytes decreased rapidly and blast cells differentiated to segmented neutrophils after chemotherapy. The antileukemic effects of Homoharringtonine mainly depended on inhibiting protein synthesis to inhibit proliferation, induce differentiation, and promote apoptosis of leukemic cells, leukemia stem cells included too.[11–15] Moreover, Chen et al[9] found that As_2O_3 mediated a dual effect on APL cells in a dose-dependent manner in vitro and vivo studies. A higher concentration of As_2O_3 (0.5–2.0 pmol/L) led to apoptosis which was associated with mitochondrial pathway and the degradation of PML-RARα oncoprotein, while a lower concentration of As_2O_3 (0.1–0.5 pmol/L) induced partial differentiation related to granulocytic pathway to some extent. We observed the leukocytes reduction and blast cells differentiation after chemotherapy. Additionally, Chinese investigators reported that all-trans retinoic acid could induce differentiation in t(8;21) AML leukemic cells.[16] But the underlying mechanisms of Homoharringtonine and As_2O_3 are still needed to be elucidated in AML1-ETO positive cell lines.

5. Conclusion

To conclude, the regimen of Homoharringtonine coupled with As_2O_3 may bring substantial effects on elderly AML-M2 patients, which must rely on randomized controlled trials on many more patients to confirm. Besides, more experiments on AML1-ETO – expressing cell lines should be carried out to understand the potential mechanisms.

Author contributions

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Writing – review and editing: Zhipeng He, Xueting Xiao, Yanhong Lu, Yong Wu.

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