Treatment of STAT5b-RARA positive acute promyelocytic leukemia by Venetoclax combining with homoharringtonine, cytarabine: A case report and literature review

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Abstract

Introduction: Acute promyelocytic leukemia (APL) is mostly due to the chromosome translocation t (15; 17) (q22; q12), leading to the formation of *PML-RARA* fusion protein. Some patients carried rare translocation involving RARA gene, who were called variant APL caused by RAR family (RARA, RARB, and RARG) and partner genes. *STAT5b-RARA* was a rare type of molecular genetic abnormality with unfavorable prognosis which have been reported in only 18 cases in variant APL. Knowledge of *STAT5b-RARA* (+) APL treatment is still limited.

Case report: We presented a 38-year-old female variant APL case, who was *STAT5b-RARA* positive detected by reverse transcription polymerase chain reaction. The patient failed to respond after four-drug combined induction chemotherapy: idarubicin, cytarabine, all trans retinoic acid, and arsenic trioxide (As_2O_3). Then, the patient was re-induced with azacytidine, but still failed to achieve complete remission (CR). Next, she was treated with Venetoclax combining with homoharringtonine and cytarabine as the salvage therapy and achieved CR. Later, the patient received hematopoietic stem cell transplantation after 4 cycles of consolidation therapy.

Conclusion: Venetoclax combining with homoharringtonine and cytarabine has been used as the salvage therapy in the *STAT5b-RARA* positive APL successfully.

Keywords: Acute promyelocytic leukemia (APL), Case report, Nested PCR, STAT5b-RARA, Venetoclax

1. INTRODUCTION

Classic chromosome translocation t (15; 17) (q22; q12) is hard to be found in approximately 1% to 2% patients with typical morphology of acute promyelocytic leukemia (APL); *PML-RARA* fusion transcript cannot be detected by fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR).[1,2] These specific subgroup patients were defined as variant APL or resembling APL. *STAT5b-RARA* was a rare molecular genetic abnormality with an unfavorable prognosis in variant APL.[3] However, knowledge of its treatment is still limited. Here, we reported a patient with *STAT5b-RARA* fusion gene enrolled by the Institute of Hematology and Blood Diseases Hospital, who successfully treated by the salvage regimen including Venetoclax plus traditional chemotherapy.

2. CASE REPORT

The patient, 38 years old female, was admitted to a local hospital due to blood abnormality during her pregnancy. Her initial full blood count revealed white blood cell (WBC) count of 16.5×10^9/L with 86% of blast cells, hemoglobin (HGB) of 4.7 g/dL, and platelet count (PLT) of 30×10^9/L. The coagulation function was normal. Bone marrow smears revealed 58.5% blast cells. The immunophenotypic results of flow cytometry showed that the abnormal cell population accounted for 85.62% in all the nucleated cells, expressing CD33, CD13, CD34, and HLA-DR, and CD117, MPO, CD64 partially positive, and dimCD123. Chromosome karyotype result showed 46, XX, del (6) (q22), - 7, - 14, + mar2 [20]. Multiple PCR of 43 leukemia fusion genes showed that *STAT5b-RARA* was positive. Quantitative calculation: *STAT5b-RARA* copy number was 12809419, *STAT5b-RARA* copy number/ABL1 copy number × 100% = 238.435%. This patient was diagnosed as "Acute

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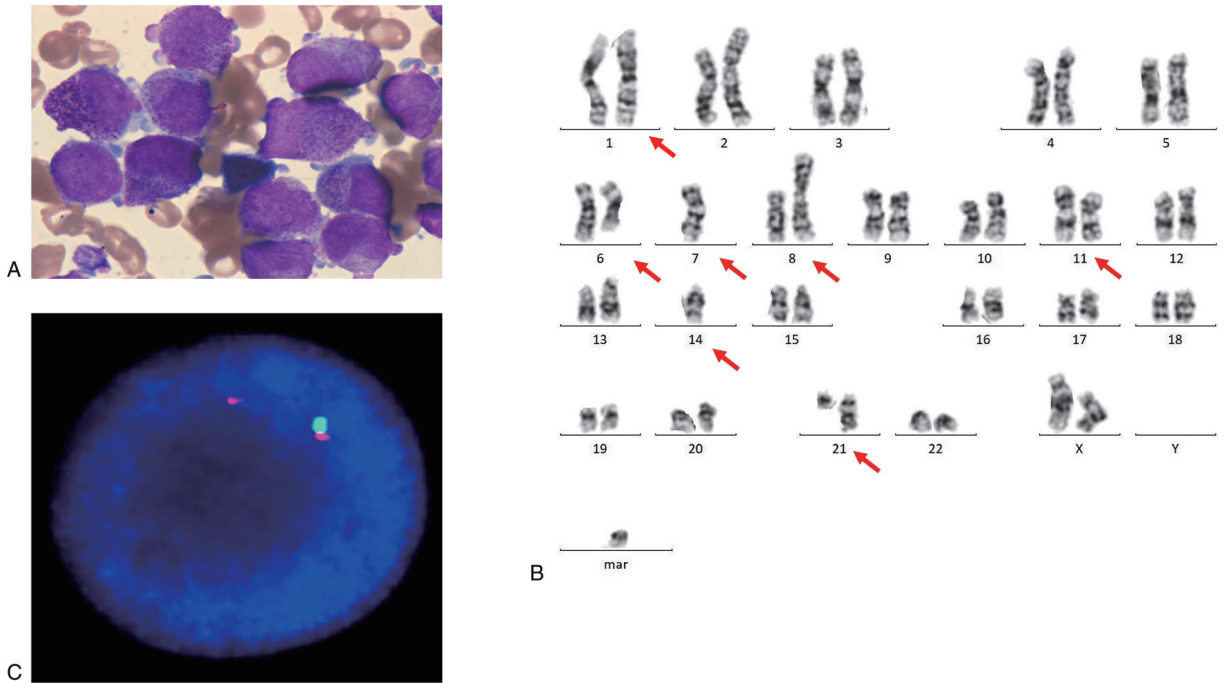

Figure 1. Morphology, cytogenetic and molecular analysis of the *STAT5b-RARA* fusion gene. (a) Morphology re-examination before Venetoclax plus HA treatment. (b) Chromosome analysis before Venetoclax plus HA treatment. (c) The probes 3′ RARA (green) and 5′ RARA (red) are used in the dual-color break-apart fluorescence in situ hybridization (FISH) analysis before Venetoclax plus HA treatment, in which RARA translocation is detected as split signals in *STAT5b-RARA* (+) patient.

promyelocytic leukemia with *STAT5b-RARA* (+)" based on the molecular data.

Firstly, the patient began to receive four-drug combined chemotherapy, including idarubicin (12 mg/m^2/d × 3 days), cytarabine (100 mg/m^2/d × 2 days), all trans retinoic acid (ATRA) (50 mg/d × 14 days), and arsenic trioxide (10 mg/d × 10 days). Reexamination of blood routine examination suggested WBC 0.39×10^9/L, HGB 7.5 g/dL, and PLT 41×10^9/L at 21st day after discontinued chemotherapy. Bone marrow examination implied that the patient failed to achieve complete remission (CR). Azacytidine (100 mg/d × 7 days) was given to the patient subsequently as the re-induction therapy.

After two courses treatment, the patient was transferred to Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. Clinical data of the patient in our center is shown in Figures 1 and 2. The blood count was as follows: WBC 1.73×10^9/L, HGB 6.8 g/dL, PLT 51×10^9/L; bone marrow smear showed that the proportion of blast cells was 54% (shown in Fig. 1a). The chromosomes was complex karyotype with 45-46, XX, inv (1) (p22p13), del (6) (q21), -7, add (7) (q11.2), add (8) (p11.2), i(8) (q10),add(11)(q25), -14,-18,add(21)(21), +r, +mar[cp20] (shown in Fig. 1b). Multiple PCR of 43 leukemia fusion genes also reflected that *STAT5b-RARA* was positive. The percentage for two color RARα (3′ RARA Green/5′ RARA Red) positive signal of FISH was 67% with the threshold <2.1% (shown in Fig. 1c). *PML-RARA* probe was negative in this case. We verified the *STAT5b-RARA* using nested PCR: STAT5b-F1: 5′-GCCGTGCCTGACAAAGT-3′; RARA-R1: 5′-TCTTCTTGTTTCGGTCGTT-3′; STAT5b-F2: 5′-ACATCTCAAGCCTCATTGGA-3′; RARA-R2: 5′-TGTTT CGGTCGTTTCTCAC-3′. PCR products were directly sequenced using an ABI 3730 XL DNA Analyzer (Applied Biosystems, Foster City, CA).

The patient began to receive B-cell lymphoma-2 [BCL-2]) inhibitor Venetoclax (100 mg d1; 200 mg d2–14), homoharringtonine (2 mg/d, d4–10) and cytarabine (100 mg/d intravenous d4–10) as salvage regimen (Ven + HA). During the myelosupression period, the patient suffered from grade 4 hematological toxicity (including leukopenia, thrombocytopenia), and non-hematological toxicity including grade 2 proteinuria and grade 1 fever. Functions of liver and kidney were almost normal. No more discomfort complains. Peripheral blood examination restored to roughly normal state WBC 3.8×10^9/L, HGB 11.6 g/dL, PLT 101×10^9/L at the 25th day of chemotherapy discontinue. Bone marrow smears showed granulocytic, erythroid, and megakaryocytic hematopoietic recovery with the blasts <5%. She was defined CR. We reexamined *STAT5b-RARA* fusion gene using RT-PCR, the result turned into negative. Later, the same regimen was repeated 2 courses as consolidation.

Then, BCL-2 inhibitor Venetoclax (400 mg d1–7) combining cytarabine (3 g/d intravenous d2–4) was given to the patient for 2 cycles. The patient complains no significant syndrome expect of fatigue during the consolidation chemotherapy. The levels of protein, glucose, chlorides, and cells in cerebrospinal fluid remained normal range during the whole process of treatment. The patient remains CR status for 6 months up-till now. She received hematopoietic stem cell transplantation (HSCT) recently.

3. DISCUSSION

APL is mostly due to the chromosome translocation t (15; 17) (q22; q12),[1] leading to the formation of *PML-RARA* fusion gene. Some patients carried rare translocation involving RARA gene, which were called variant APL caused by RAR family (RARA, RARB, and RARG) and partner genes.[4]

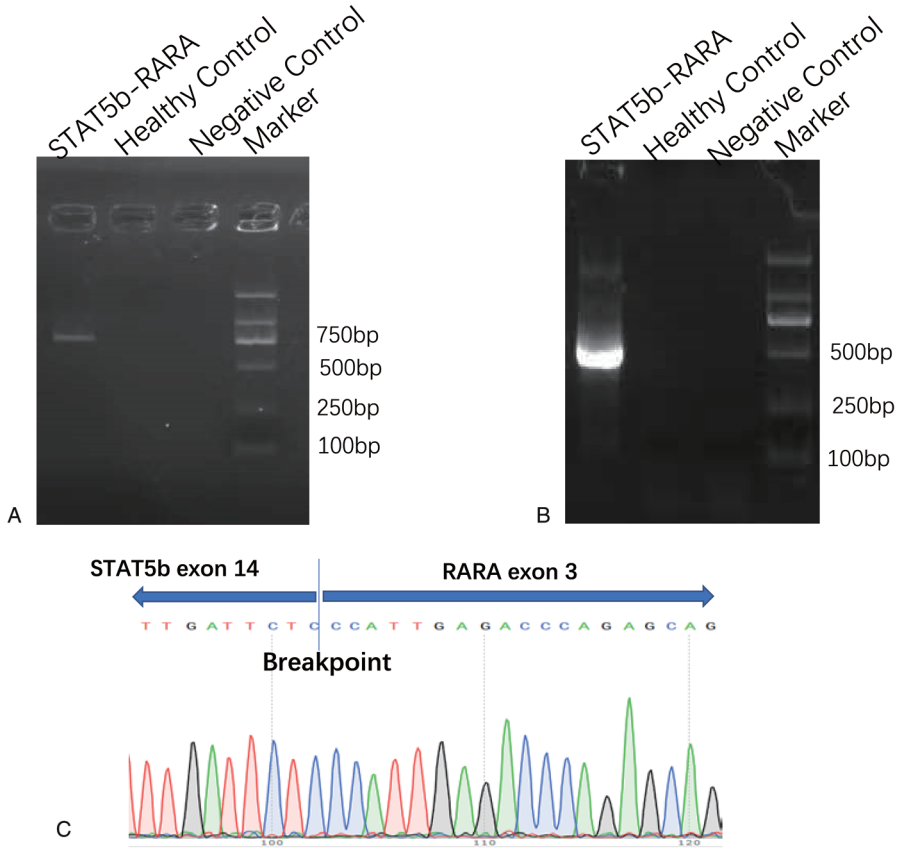

Figure 2. Results of *STAT5b-RARA* detected by nested PCR. (a) The target DNA was amplified by the first pair of primers (called external primers) with the amplicon of 753 bp. (b) The target DNA was amplified by the second pair of primers (called internal primers) with the amplicon of 470 bp. (c) RT-PCR sequencing results show the fusion between STAT5b exon 14 and RARA exon 3.

The partner genes involved with RARA include *PLZF*, *NPM1*, *NUMA1*, *STAT5b*, *PRKAR1A*, *FIP1L1*, *BCOR*, and *TBLR*. Of note, *STAT5b-RARA* positive APL only accounted for 0.28% in all the patients. It was characterized by insensitivity to arsenide and retinoic acid.[3] It was resistant to the standard chemotherapy regimen and suggested dismal prognosis too.[3,5]

This patient with *STAT5b-RARA* positive APL was induced with idarubicin, cytarabine, retinoic acid, and arsenide in the first course. Azacytidine was used in the second course. But the patient did not achieve CR. In the third course of treatment, Venetoclax combined with traditional chemotherapy (Ven + HA) was tentatively used and the patient reached morphological and molecular remission up till now.

So far, 18 cases with *STAT5b-RARA* positive APL (including our patient) have been reported in literature review.[6,7] They include 15 male and 3 female patients, with the median age 39 (17–67) years old and median WBC at diagnosis was 6.1 (1.6–77.8) $\times 10^9$/L. Except for 1 patient died during ATRA induction treatment without evaluation of outcome, the overall CR rate of the rest 17 cases was 64.7% (11/17). The median overall survival time was 9.5 (0–53) months and disease-free survival time was 3 (0–24) months. Of these patients, 5 reached CR after 1 course induction treatment, including ATRA (2 cases), ATRA + IA (2 cases), and ATRA + IA (idarubicin + cytarabine) + As_2O_3 (1 case). Other 3 patients achieved CR after 2 courses chemotherapy. The effective regimens were as follows: DA (doxorubicin + cytarabine) + mitoxantrone (MIT) + VP-16; FLAG (fludarabine, cytarabine, and Granulocyte Colony-stimulating Factor); DA. The remaining 3 patients who were insensitive to 2 courses of induction treatment were successfully treated by salvage regimen separately: 1 patient achieved CR by decitabine combining to AA (aclacinomycin + cytarabine)/IA for 6 cycles reported by Wang et al,[7] 1 case applied FLAG + IA + ATRA regimen and our case achieved CR with Ven + HA regimen.

However, 6 patients failed to reach CR through chemotherapy with the 2 (1–3) median courses treatment. Among them, 2 cases achieved morphological remission by HSCT. The rest 4 cases did not reach remission during the whole period.

Currently, the treatment of *STAT5b-RARA* is merely focusing on ATRA ± As_2O_3 ± anthracyclines and cytarabine; physicians had not looked further into target drugs combined traditional chemotherapy. Based on multicenter clinical data, Venetoclax combining with hypomethylating agents or low dose cytarabine is considered appropriate choice for untreated intensive-induction therapy ineligible AML patients.[8] Besides, several clinical trials revealed that Venetoclax plus traditional chemotherapy increased overall remission rate of AML patients. The efficiency and safety of modified intensive chemotherapy (idarubicin 12 mg/m^2/d d2–3, cytarabine 100 mg/m^2/d, d1–5) combining with Venetoclax was proved for elderly AML patients.[9] The regimen of Venetoclax (400 mg d2–8) combining CLAG-IDA (cladribine + idarubicin + cytarabine) as induction therapy achieved high CR rate (94%) in untreated AML population.[10] Venetoclax combined FLAG-IDA (fludarabine + idarubicin + cytarabine) as induction and consolidation therapy achieved measurable residual disease-negative composite CR in 96% of newly diagnosed-AML and

69% of relapsed or refractory-AML patients in a phase II trial.[11] Venetoclax showed better effectiveness though Bcl-2 expression of patients was not detected routinely in these trials.

Interestingly, we found several cases treated with Venetoclax-based therapy: Liu et al[12] reported a novel *HNRNPC-RARA* fusion in variant APL who was sensitive to Venetoclax-based therapy. Song et al[13] identified THRAP3 as novel RARA fusion gene. This patient was salvaged by low-dose Venetoclax and decitabine.

This empirical attempt may lay a foundation for variant APL with *STAT5b-RARA* positive treatment in the future. The underlying mechanism is worth further exploration.

4. CONCLUSION

In summary, we attempted Venetoclax combining HA regimen as salvage therapy of the *STAT5b-RARA* positive leukemia for the first time and achieved ideal result. This attempt provides a promising treatment of *STAT5b-RARA* (+) APL, though larger groups of patients are needed to be verified.

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