Successful Haploidentical Hematopoietic Stem Cell Transplantation with Azacitidine and Venetoclax Maintenance Therapy for Acute Myeloid Leukemia with *NUP98-RARG* Gene Fusion

NUP98-RARG Gen Füzyonlu Akut Myeloid Lösemide Azasitidin ve Venetoclax İdame Tedavisi ile Başarılı Haploidentik Hematopoetik Kök Hücre Nakli

Jiaojiao Yuan, Renzhi Pei, Ying Lu

The Affiliated People's Hospital of Ningbo University, Department of Hematology, Ningbo, Zhejiang, China

To the Editor,

NUP98-RARG-positive acute myeloid leukemia (AML) has morphological, immunophenotypic, and clinical manifestations of acute promyelocytic leukemia but lacks t(15;17)(q24;q21)/*PML-RARA* fusion [1]. Almost all of these subtypes of AML exhibit resistance to all-trans retinoic acid [2,3] and have poor prognosis [4]. Alkaloid-based chemotherapy regimens may be beneficial for AML with *NUP98/RARG* fusion [5,6]. However, the value of haploidentical hematopoietic stem cell transplantation (HID-HSCT) in AML patients with *NUP98-RARG* rearrangement is unknown due to the limited number of reported cases.

A 39-year-old female was admitted due to skin ecchymosis. Her D-dimer level was 16020 ng/mL (reference range: 0-256 ng/mL). Morphological examination of bone marrow (BM) smears revealed hypercellularity, with 87% abnormal promyelocytic granulocytes (Figure 1A). A peroxidase-stained BM smear showed strong positivity (Figure 1B). Immunophenotypic analysis revealed that the leukemic cells were positive for myeloperoxidase, CD13, CD33, CD117, CD71, and HLA-DR and negative for CD34, CD11b, and CD38 (Figure 1C). However, detection results for the *PML-RARA* fusion transcript and karyotype analysis of typical t(15;17) were negative. RNA sequencing identified the *NUP98-RARG* fusion transcript. The karyotype of G-banding showed 46,XX,t(11;12)(p15;q13),t(15;21)(q11.1;q21) in 20/20 analyzed metaphases (Figure 1D). Reverse transcriptase polymerase chain reaction (PCR) was then performed on the BM sample with primers 5'-CTGTTGGTTCGACCCTG-3' and 5'-GGACATGCCCACTTCG-3', which further suggested the presence of *NUP98-RARG* fusion. To identify the breaking point of *NUP98-RARG*, the PCR product was subjected to Sanger sequencing. Sequence analysis of the *NUP98-RARG* fusion transcript revealed that *NUP98* exon 12 was fused in-frame to *RARG* exon 4 (Figure 1E). Finally, the patient was diagnosed with AML with *NUP98-RARG* gene fusion.

The patient was treated with venetoclax in combination with homoharringtonine, cytarabine, aclarubicin, and granulocyte

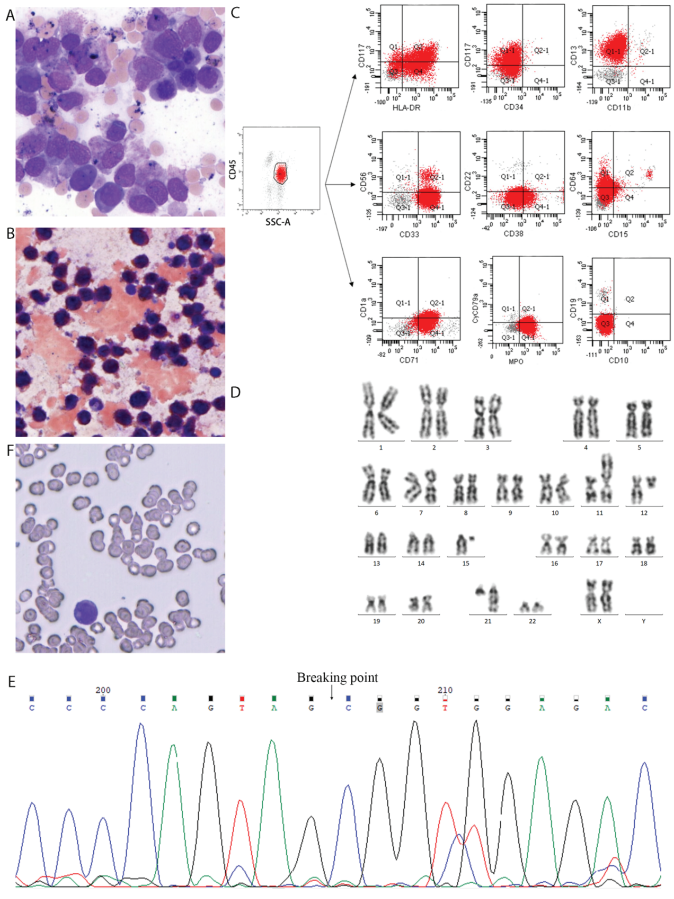

Figure 1. The morphological (**A, B**: bone marrow smear stained with Wright-Giemsa, 400^{x}), immunophenotypic (**C**), and cytogenetic (**D**) analysis results of bone marrow cells at diagnosis. (**E**) Sanger sequencing for *NUP98-RARG* PCR products; (**F**) bone marrow morphology upon complete remission (bone marrow smear stained with Wright-Giemsa, 400^{x}).

colony-stimulating factor (HCAG) chemotherapy. Complete remission (CR) was achieved on the 14th day of treatment according to the evaluation of BM morphology (Figure 1F), and minimal residual disease as assessed by flow cytometry was

negative. *NUP98-RARG* gene fusion was negative according to next-generation sequencing after one course of consolidation chemotherapy identical to the induction regimen. The patient proceeded with myeloablative HID-HSCT from a half-matched related donor using conditioning therapy based on the Beijing Protocol [7,8]. The quantities of infused mononuclear cells and CD34+ cells of the grafts were $7.8x10^8$/kg and $3.1x10^6$/kg, respectively. The durations of neutrophil and platelet engraftment were 12 days and 15 days, respectively. She received post-transplant maintenance with azacitidine (75 mg/m^2/day on days 1-5) and venetoclax (400 mg/day on days 1-14) for two cycles. The patient refused to undergo any further treatment for personal reasons. She remained in CR and negative for *NUP98-RARG* gene fusion, and overall survival had surpassed 20 months at the last follow-up.

Our case suggests that HID-HSCT with azacitidine and venetoclax maintenance therapy could be a highly efficient treatment option for AML with *NUP98-RARG* gene fusion.

Keywords: Acute myeloid leukemia, *NUP98-RARG*, Haploidentical hematopoietic stem cell transplantation

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Address for Correspondence/Yazışma Adresi: Ying Lu, M.D., The Affiliated People's Hospital of Ningbo University, Department of Hematology, Ningbo, Zhejiang, China
E-mail : ly20210927@163.com ORCID: orcid.org/0000-0002-2509-9209

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