Successful Complete Remission with Chidamide, Venetoclax, and Azacytidine in Relapsed Acute Myeloid Leukaemia Associated with Plasmacytoid Dendritic Cells

Sir,

Acute myeloid leukaemia associated with plasmacytoid dendritic cells (pDC-AML) is regarded as a distinct disease different from blastic plasmacytoid dendritic cells neoplasm (BPDCN).[1] pDC-AML was formally recorded in the 2022 WHO classification.[1] The morphological features of pDC-AML are two cohorts of neoplastic cells, plasmacytoid dendritic cells (pDCs), and blasts, which are related to each other.[1] The immunophenotypic features of pDC-AML are CD34+, CD117±, and CD123+ on blasts and CD4+, CD123+ (high), CD303+ (high), and cTCL1+ (low), without expression of CD56 on pDCs.[1] Nowadays, the diagnosis of pDC-AML is mainly based on morphology and immunophenotype of neoplastic cells.[1] However, the treatment of pDC-AML, especially the relapsed cases, remains unclear.

Herein, the researchers report a clinical case of a relapsed pDC-AML patient achieving complete response (CR) with chidamide, venetoclax, and azacytidine (VA). In May 2021, a 45-year male patient was admitted to our hospital with diffuse erythematous skin papules and macules, enlarged lymph nodes in the bilateral neck, supraclavicular fossa, axilla, groin, mesenteric and left posterior perihepatic space, as well as splenomegaly. Ground-glass opacities were detected on imaging of bilateral lungs. Blood tests showed white blood cell count of 21.59 × 10^9/l with 75.1% neutrophil-granulocytes, 9.1% monocytes and 1% blasts, haemoglobin of 10.8 g/dl, and platelet count of 45 × 10^9/l. Bone marrow (BM) smear showed 20.5% myeloblasts and 24.5% pDCs with cytoplasmic pseudopodia and small vacuoles. BM flow cytometry showed 12% blasts that expressed CD34+, CD117+, CD123+, HLA-DR+, CD13+, CD33+, CD38+, and TdT+, and 13% pDCs that expressed CD4+, CD123+ (high), CD303+, CD38+, and HLA-DR+, without CD56 expression. Chromatin analysis showed a karyotype of 46, XY [20]. Using sorted cell populations, whole genome sequencing of blasts and pDCs showed the same mutations of *NRAS*, *SUZ12*, *ASXL2*, *NOTCH1*, *etc*. except *FLT3* mutation which was found in blasts. Biopsies of skin papules and cervical lymph nodes consistently showed infiltration of pDCs that expressed CD56-, CD4+, CD123+, and CD38+. Based on these findings, a diagnosis of pDC-AML was made.

The patient received two cycles of VA (venetoclax, 100 mg/d day 1; 200 mg/d day 2; 400 mg/d from day 3 to 28; azacitidine 75 mg/m^2 subcutaneously on day 1 to 7 in 28-day cycle). After two cycles, CR1 based on skin, lymph nodes, lungs, spleen, and BM was achieved. BM flow cytometry did not detect the previous blasts and pDCs. BM minimal residual disease (MRD) was negative with flow cytometry. *NRAS*, *SUZ12*, *ASXL2*, and *NOTCH1* mutations in blasts and pDCs were not also detected.

Unfortunately, the follow-up BM smear showed 22.5% myeloblasts and 4.0% pDCs after three months. *NRAS*, *SUZ12*, *ASXL2*, and *NOTCH1* mutations in blasts and pDCs were detected again. Therefore, the patient was diagnosed with relapsed pDC-AML. Although two cycles of VA and one cycle of idarubicin plus cytarabine were used successfully, BM smear of the patient showed progressive disease with 29.0% myeloblasts and 2.5% pDCs. Based on *NOTCH1* mutation in blasts and pDCs and chidamide overcoming resistance to VA,[2] the patient received one cycle of chidamide and VA (chidamide 30 mg twice per week day 1 to 14; venetoclax, 100 mg/d day 1; 200 mg/d day 2; 400 mg/d from day 3 to 28; azacitidine 75 mg/m^2 subcutaneously on day 1 to 7 in a 28-day cycle). The BM smear showed only 2.5% myeloblasts and the blood test without abnormal value showed CR2.

The treatment of this patient was based on the following settings. Venetoclax can induce blast apoptosis in AML.[3] 5-azacytidine (azacytidine) enhances venetoclax-induced apoptosis in AML.[4] A recent case reported that one pDC-AML patient got CR from VA.[5] Wang *et al*. reported that chidamide combined with VA could overcome resistance to VA in relapsed/refractory AML.[2] Xi *et al*. found that chidamide could overcome *NOTCH1* mutation for making T-cell acute lymphoblastic leukaemia (T-ALL) patients achieve better effect.[6] Meanwhile, the *NOTCH1* mutation was again detected in this case of relapsed pDC-AML. Fortunately, this relapsed patient used one cycle of chidamide combined with VA and achieved CR. To the best of our knowledge, this is the first report of implementing a chidamide combined with VA and enabling relapsed pDC-AML patient to achieve CR after one course.

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