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CASE REPORT

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Decitabine for the Treatment of Juvenile Myelomonocytic Leukemia with CBL Mutation: A Case Report and Literature Review

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Abstract

Juvenile Myelomonocytic Leukemia (JMML) is an aggressive clonal hematopoietic disorder of infancy and early childhood. CBL family proteins negatively regulate receptor signal transduction by distinct mechanisms. Almost 10-15% of JMML patients carry CBL germline mutation. Once the gene is destroyed by hypermethylation mutation, it will lead to a tumor, CBL syndrome, and even vasculitis. This mutation has a high rate of spontaneous resolution of disease, while some patients have progression of the disease. At present, there is no standard treatment plan for these patients. Here we report the first case with CBL (C401Y) mutation treated with Decitabine. He was treated with Decitabine and achieved clinical Complete Remission (CR) after three cycles of treatment. Unfortunately, the patient's vasculitis symptoms relapsed two months after withdrawal of decitabine. Nevertheless, Decitabine plays a significant role in controlling symptoms. It is deserved to further explore if hematopoietic stem cell transplantation should be bridged to demethylation therapy for these children to avoid the occurrence of severe vasculitis symptoms.

Keywords: JMML; CBL mutation; Vasculitis; Demethylation therapy; Decitabine

Background

Juvenile Myelomonocytic Leukemia (JMML) is a myeloproliferative disorder of childhood characterized by an excessive proliferation of cells of monocytic and granulocytic lineages with an incidence rate of 1.2 per million per year [1]. The main clinical manifestations of JMML were splenomegaly, thrombocytopenia, peripheral monocyte proliferation, elevated hemoglobin F, and sensitivity to Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) [2-4]. The spectrum of mutations includes NF1, NRAS, KRAS, PTPN-11, and CBL. Among them, about 10-15% of the patients carry CBL germline mutations [5-7]. In recent years, it is considered aberrant methylation of specific genes leads to abnormal signal pathways in patients with JMML, and the degree of methylation is closely related to the prognosis and complications of patients. Demethylation therapy may relieve patients' symptoms and prolong survival time [7,8]. Here we report a JMML patient with CBL mutation. Including his basic condition and the therapeutic effect.

Case

A six months old boy was diagnosed with JMML because of the whole-body hemorrhagic spot, cough, repeated pulmonary inflammation. The spleen was palpable 2cm below the costal margin. Blood routine showed leukocytosis (53.4 × 10^9/L), thrombocytopenia (77 × 10^9/L), and striking monocytosis (15.49 × 10^9/L). The Bone Marrow (BM) was revealed 3% blast cells. No BCR/ABL fusion transcript and karyotype on BM cells was 46, XY. We detected CBL (C401Y) mutation in the patient's fingernails. The same mutation was found in his father's peripheral blood, but he had no clinical symptoms (Figures A and B). Then we treated him with a DNA-hypomethylating agent which takes a course every 4 weeks with 5 days of continuous decitabine (20mg/m^2/d). After three courses of treatment, the patient's spleen was significantly shrinking, with no obvious granulocytopenia no other inflammation and hematopoietic function returned to normal. According to the evaluation criteria, he achieved complete remission. However, shortly after drug withdrawal, he developed splenomegaly again, accompanied by enteritis, axillary abscess, striking monocytosis, thrombocytopenia. Further vascular events occurred six months later that he developed inflammatory optical neuropathy in both two eyes, resulting in the loss of visual acuity. We treated him with glucocorticoid and gamma globulin to restore his vision but failed.

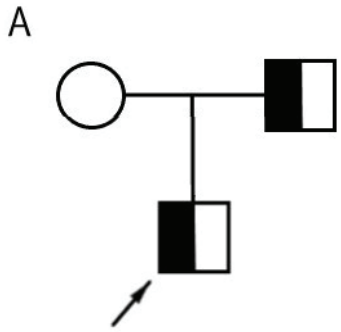

Figure A: According to the genetic pedigree map of the patient, the patient is a proband, his father carries the CBL gene mutation, and his mother has a normal genotype.

B	The results of gene sequencing		
	Specimen source	**Result**	**Diagnosis**
Father	Peripheral blood	CBL C401Y	None
Mother	Peripheral blood	None	None
Patient	Nail	CBL C401Y	JMML

Figure B: Genetic test results of patients and their relatives..

Discussion

JMML is characterized by excessive proliferation of monocytes and granulocytes, and the formation of an abnormally high number of granulocyte-macrophage colonies in the culture of low concentration of GM-CSF. The leukemia cells can infiltrate the lung, liver, and spleen, leading to early respiratory insufficiency, hepatosplenomegaly, bleeding tendency, and even the possibility of transformation into Acute Myeloid Leukemia (AML), which may lead to death in severe cases [9,10]. Without allogeneic Hematopoietic Stem Cell Transplantation (HSCT), the median time of survival from diagnosis is less than two years. CBL proto-oncogene products negatively regulate the RAS signal pathway by promoting the degradation of activated receptor tyrosine kinase. The mutation destroys the original function, which leads to the occurrence of myeloid tumors [10]. Because of the tendency of spontaneous remission, the mutation represents a good prognosis. It is suggested that we can wait for observation and then undergo chemotherapy or hematopoietic stem cell transplantation if there is chromosome aberration or disease progression [5,11,12].

Through genetic testing, we found there was healthy individual in his family who carried CBL mutation (the patient's father), but there were no clinical manifestations. The patient's clinical manifestations may be related to loss of heterozygosity although his genotype is heterozygous [8,13]. Based on the degree of DNA methylation, CBL mutations were classified as germline mutations with Low Methylation (LM), which means that such patients usually have a higher survival rate [14-16]. But animal experiments demonstrated that CBL mutation could lead to severe vasculitis in mice, which is characterized by significant thickening of intima and adventitia, accompanied by a large number of T cell infiltration [5,17]. So for patients with progressive disease, germline mutations will persist even if complete remission is achieved after treatment, and vasculitis is also more likely to occur at a later stage of the disease [18].

In our case, it is considered that the child has vasculitis at the same time, which affects organ function. So, we suggested demethylation therapy. Decitabine is an effective specific inhibitor of DNA methylation, which inhibits the growth of tumor cells by irreversibly inhibiting the proliferation of S-phase DNA methyltransferase. Enhance the immunogenicity of tumor cells, make them easy to be detected and cleared by the host immune system, and prevent drug resistance [6,10]. Therefore, we put forward for the first time in decitabine for low-dose and short-term treatment of CBL mutation in JMML. After three courses, he reached Complete Remission (CR) according to the evaluation criteria, especially platelets returned to the normal range [18]. But unfortunately, his symptoms relapsed due to the germline mutation and even developed into irreversible vasculitis leading to binocular blindness.

Treatment experience has proved that although CBL mutation is a hypomethylation change, demethylation therapy can effectively control clinical symptoms and significantly improve the quality of life of patients with vasculitis. Since no report of C401Y mutation has been found, its mechanism and whether demethylation therapy combined with hematopoietic stem cell transplantation to avoid vasculitis remains to be further discussed.

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Conflict of Interest Statement

The authors declare no competing financial interests.

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