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Case Report Open Access

The First Case of Decitabine Successfully in Treatment of Atypical Chronic Myeloid Leukemia with CEBPA Double Mutation

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Abstract

Background: Atypical chronic myeloid leukemia (aCML) treated with decitabine is never reported.

Methods: We admitted a 69-year-old man with splenomegaly, hyperleucocytosis, thrombocytopenia and anemia, then morphology, immunology, cytogenetics and molecular biology analysis of bone marrow were performed and the diagnosis of aCML was made. The patient was initially treated with decitabine chemotherapy (20 mg/m^2×5 days). The patient achieved complete hematology and morphologic remission after three cycle's treatment.

Results: The data demonstrated that the diagnosis was aCML, which may be misdiagnosed easily. The patient responded very well to decitabine.

Conclusion: This case provides evidence that decitabine is effective for therapy in aCML, and demonstrated a new safety and efficacy strategy in the management of other myeloproliferative diseases.

Introduction

Atypical chronic myelogenous leukemia, aCML is a subtype of myelodysplastic/myeloproliferative diseases (myelodysplastic/chronic myeloproliferative syndromes, MDS/MPN), it occurs in the elderly, the incidence rate about 1/100, 000, or less [1]. In brief, aCML is characterized by peripheral leukocytosis, circulating immature granulocytes, obvious abnormalities, and abnormal clone cells without Ph chromosome and bcr/abl fusion gene [2]. Overall, aCML is generally associated with poor outcome, and no special drug has so far proved to be effective in this disorder. In this report we summarize our experience with decitabine (5-aza-2-deoxycytidine) in a patient diagnosed with aCML.

Case Report

We admitted a 69-year-old man for anorexia, fatigue and shortness of breath for three months and dizzy ten days. Physical examination revealed pallor and mild splenomegaly and needle-like bleeding point. Laboratory examinations showed hyperleukocytosis with WBC 27.2×10^9/L (reference range, 4-10×10^9/L), differential count of neutrophil 78.2%, monocytes 1.9%, basophilic granulocytes 0.3%, thrombocytopenia with PLT 17×10^9/L (reference range, 100-300×10^9/L), and hemoglobin of 63 g/L (reference range, 120-150 g/L). Then the Bone Marrow Aspirate (BMA) was performed. Morphology of BMA showed a hypercellular marrow with myeloblasts 7%, promyelocytes 7.5%, myelocytes 12.5%, metamyelocytes 24.5%, NAP integral is zero. The proportion of lymphocytes significantly reduced. Immunophenotype analysis of BMA showed myeloid cell about 97.5% of nuclear cells, including blast cells (4.5%), distribution is relatively concentrated, mainly myeloid expression; Mononuclear cells (1.5%), mature phenotype; the proportion of Granulocyte increased , account for about 91.5%, and some of these cells presented dysplasia. Lymphocyte percentage decreased obviously. Cytogenetic analysis revealed a normal karyotype: 46, XY. Molecular biology analysis of BMA: PDGF fusion gene negative, JAK2 mutation negative and CEBPA double mutation positive. The patient was diagnosed with aCML and treated with decitabine (20 mg/m^2×5 days). The patient's Hematologic improvement was achieved after one cycle treatment, and peripheral blood count returned to normal level, bone marrow showed no blast and dysplasia cells after three cycles of therapy (Figure 1).

Discussion

An aCML is a syndrome of abnormal chromatin clumping. Peripheral blood smears showing leukocytosis, immature granulocytes, and neutrophils with abnormal condensation of the nuclear chromatin. The 2008 WHO diagnostic criteria for aCML [3] is basically a neutrophilic leukocytosis with dysgranulopoiesis and circulating immature granulocytes, and its diagnosis relies on: 1) Peripheral blood leukocytosis (WBC ≥ 13×10^9/L) due to increased number of neutrophils and their precursors, with prominent dysgranulopoiesis. 2) No Philadelphia chromosome or BCR-ABL fusion gene. 3) No rearrangement of PDGFRA or PDGFRB. 4) Neutrophil precursors promyelocytes, myelocytes, metamyelocytes) are 10% of WBCs. 5) Minimal absolute basophilia; basophils usually 2% of the WBCs. 6) No or minimal absolute monocytosis; monocytes are 10% of WBCs. 7) Hypercellular BM with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages. 8) 20% blasts in blood and/or BM. This patient meets the aCML diagnostic criteria. He has mild splenomegaly and normal chromosomes, negative BCR-ABL fusion gene, peripheral blood monocytes <1.0×10^9/L, immature neutrophils in the bone marrow is 44.5%, therefore, it can be excluded the diagonosis of Chronic Myelogenous Leukemia (CML), Chronic Myelogenous Leukemia (CMML) and chronic neutrophilic leukemia (CNL). So the diagnosis of aCML was correct.

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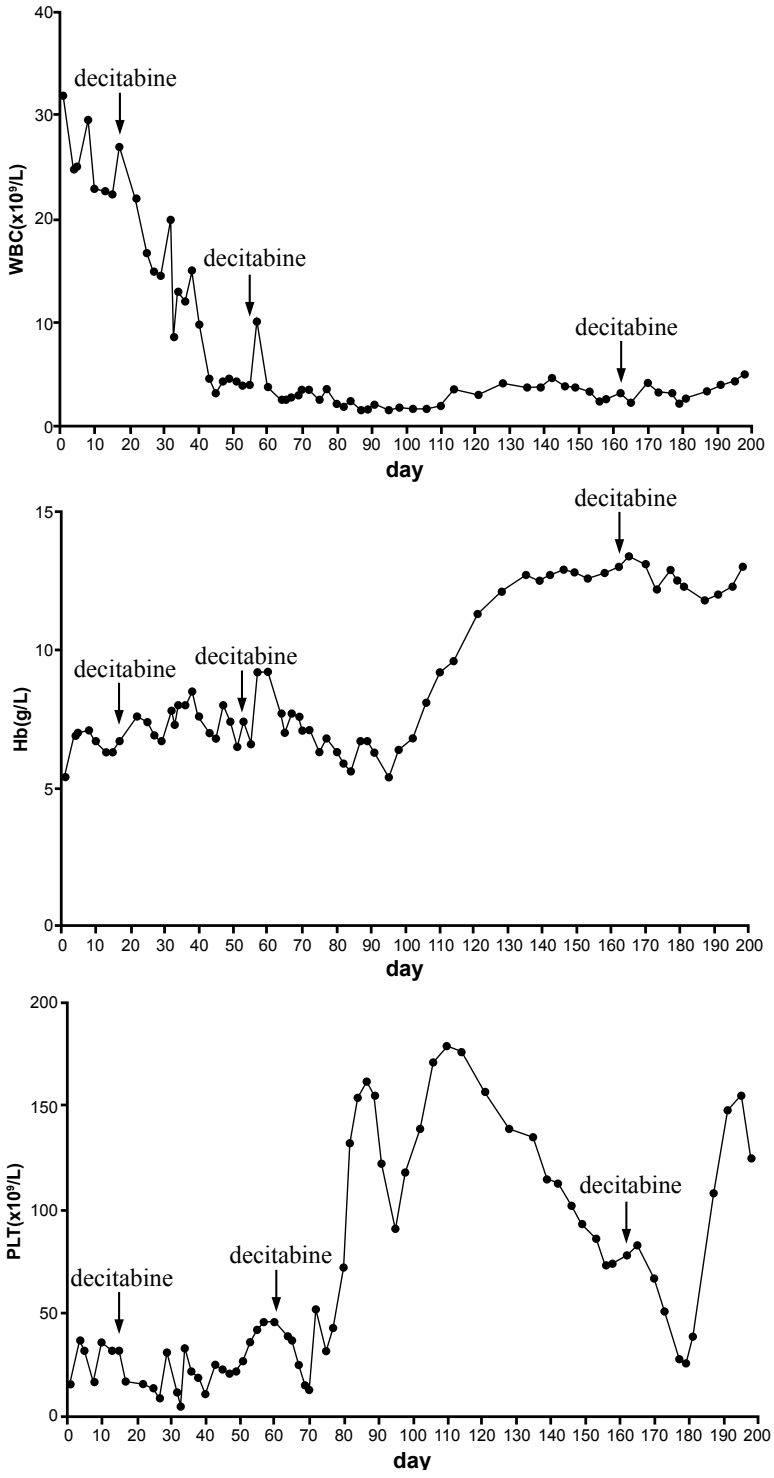

Figure 1: The level of leukocyte hemoglobin and Platelet after decitabine treatment.

Until recently, the most common karyotypic changes reported in aCML include trisomy 8 and del (20q), abnormalities involving other chromosomes such as 12, 13, 14, 17, 19 and 21 have also been described [4,5] but no specific chromosomal changes correlations with disease features were found in aCML patients. Many gene mutations have been found in aCML, such as, NRAS /KRAS (33% patients), TET2 (33% patients) CBL (10% patients), E2H2 (13% patients) and SETBP1 (25% patients) and so on [6-9] , some of which are associated with poor prognosis, but CEBPA double mutations has not been reported in aCML. In this case, the patient has normal chromosome and CEBPA double mutations, and may suggest that the CEBPA double mutations also is one molecular biology feature and associated with

good prognosis in aCML as some as in acute myeloid leukemia patients [10,11].

aCML patients showed poor prognosis when treated with conventional chemotherapy, the median survival is only 24 to 25 months [12,13]. A retrospective study in MD Anderson Cancer Center [12] found that: Age (>65 years), anemia (hemoglobin<10 g/dL), white blood cell count (WBC>50×10^9/L) are three independent factors in aCML. Koldehoff [14] confirmed that allogeneic hematopoietic stem cell transplantation (HSCT) evaluated the outcome of aCML, but most aCML patients are not suitable for HSCT for their media age >60 years [13].

Decitabine is a hypomethylating agent that can reverse the DNA methylation process and induce tumor cells differentiation or apoptosis of tumor cells to normal cells [15]. In recent years, decitabine is widely used in MDS patients, and achieved good results. A phase II study demonstrates that the response rate in the 177 patients evaluated (median age 70 years) was 49% [16]. Patients with high-risk cytogenetic abnormalities according to the IPSS risk criteria showed better overall survival than those with intermediate-risk abnormalities and a rather low toxicity profile in elderly patient group. In our case, the patient were 69 years old and not suitable for bone marrow transplantation, and then accepted chemotherapy with decitabine (20 mg/$m^2\times$ 5 days). He obtained complete hematology and morphologic remission after three cycles of decitabine. An aCML has both myeloproliferative and myelodysplastic disorders characters, which maybe result in the effective treatment with decitabine.

In conclusion, aCML is difficult to distinguish from CML, CNL and CMML, which is easy to misdiagnosis clinically. Our study suggests that the CEBPA double mutations may be associated with good prognosis in aCML. Decitabine shows obvious clinical efficacy in treatment of aCML, especially for those elder people without the chance of bone marrow transplantation, and demonstrated a new safety and efficacy strategy in the management of other myeloproliferative diseases.

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