Clinical Case Report

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Durable remission in a patient of mixed phenotype acute leukemia with Philadelphia chromosome-positive treated with nilotinib and lenalidomide

A case report

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Abstract

Rationale: Philadelphia chromosome-positive mixed phenotype acute leukemia (Ph+ MPAL) is a rare type of leukemia with poor prognosis. Tyrosine kinase inhibitors (TKIs) in combination with chemotherapy have significantly improved its remission rate. However, relapse remains the major obstacle to achieve long survival. Lenalidomide is a second-generation oral immunomodulatory drug that has been broadly applied in the treatment of various hematological malignancies.

Patient concerns: A 54-year-old Chinese male patient who complained of chest pain and fatigue for 20 days. Bone marrow aspirate examination revealed hypercellularity with 70% blast cells. Flow cytometry analysis revealed that the blast cells exhibit both myeloid and lymphoid lineage antigens. Chromosomal analysis reveals t(9;22)(q34;q11) translocation. Minor BCR-ABL fusion gene was positive.

Diagnosis: Philadelphia chromosome-positive mixed phenotype acute leukemia.

Interventions: After relapsed from routine chemotherapy plus imatinib, the therapy was switched to oral therapy with nilotinib and lenalidomide due to his feeble condition.

Outcomes: He successfully achieved long survival after oral therapy with nilotinib and lenalidomide.

Lessons: Combination of TKIs with lenalidomide may be an effective maintenance treatment regimen for Ph+ MPAL patients with minimal side effect.

Abbreviations: allo-HSCT = allogeneic hematopoietic stem cells transplantation, AML = acute myeloid leukemia, CD = cluster of differentiation, CML = chronic myeloid leukemia, CR = complete remission, Cri = CR with incomplete recovery of blood counts, HLA-DR = human leukocyte antigen DR, IL-12 = interleukin-12, IL-6 = interleukin-6, MDS = myelodysplastic syndromes, MPAL = mixed phenotype acute leukemia, MPO = myeloperoxidase, Ph^+ MPAL = Philadelphia chromosome-positive mixed phenotype acute leukemia, Ph^+ALL = Philadelphia chromosome-positive acute lymphoblastic leukemia, qPCR = quantitative polymerase chain reaction, TKIs = tyrosine kinase inhibitors, TNF-α = tumor necrosis factor-α.

Keywords: lenalidomide, mixed phenotype acute leukemia, nilotinib, Philadelphia chromosome

1. Introduction

Mixed phenotype acute leukemia (MPAL) is a rare type of acute leukemia, in which the blasts exhibit lineage specific antigens of more than 1 lineage. The incidence of MPAL is < 4% of all acute leukemia cases.[1] The Philadelphia chromosome is caused by the translocation of the *ABL* gene on chromosome 9 to the *BCR* gene on chromosome 22, thus generating a novel *BCR-ABL* fusion gene that can encode constitutively active tyrosine kinases The aberrant tyrosine kinases alter the signal pathways that regulate cell proliferation, survival and self-renewal, leading to leukemogenesis of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ALL). Philadelphia chromosome, with occurrence rates around 20% to 40%, represents the most common cytogenetic abnormality in MPAL cases.[2] Philadelphia chromosome-positive MPAL (Ph^+MPAL), which meets the diagnosis criteria for MPAL with blasts bearing t(9;22)(q34;q11) translocation in patients with no history of CML, has been recognized as a distinctive disease entity. After remission by combination of TKIs and chemotherapy, allo-HSCT has been recognized as the routine option for patients with Ph^+MPAL.[3] Nonetheless, optimal treatments for Ph^+MPAL remains in debate.

Herein, we report a case of a patient with Ph^+MPAL who has achieved durable remission for more than 5 years after treatment with nilotinib and lenalidomide.

2. Case report

A 54-year-old Chinese male was admitted due to chest pain and fatigue for 20 days on February 2012. Blood test showed that

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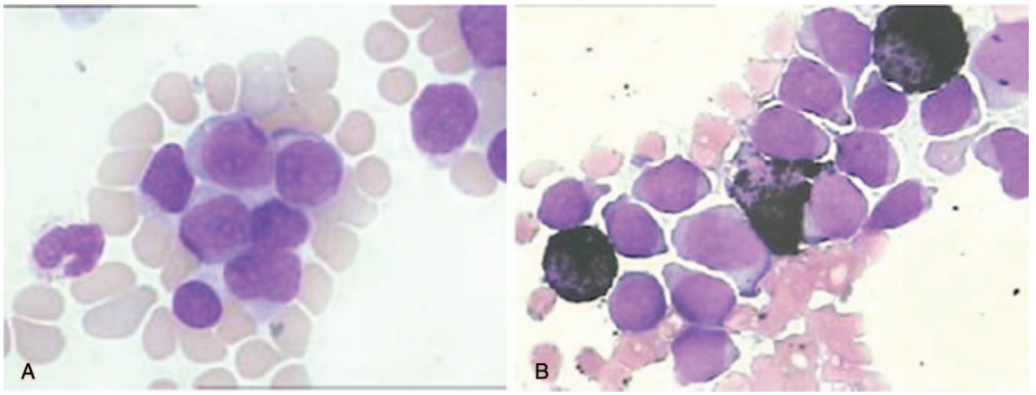

Figure 1. Blasts cells in bone marrow. (A) Bone marrow biopsy showed hypercellularity with 70% blast cells (May–Giemsa stain, ×1000 magnifications). (B) Blast cells were slightly positive by histochemical staining (Sudan Black B stain, ×1000 magnifications).

white blood cell count was 49.7×10^9/L, hemoglobin was 11.8 g/dL and platelet count was 303×10^9/L. Bone marrow biopsy showed hypercellularity with 70% blast cells, which were slightly positive for Sudan Black B (histochemical staining) (Fig. 1A and B). Flow cytometry analysis showed that the blast cells, which accounted for 71.5% of bone marrow karyocytes, were strongly positive for CD34 (93.0%), MPO (53.8%), CD33 (44.6%), CD19 (95.6%), CD22 (51.0%), CD10 (95.2%), HLA-DR (41.6%), and weakly positive for CD13 (22.6%). Chromosomal analysis of bone marrow cells found a t(9;22) (q34;q11) translocation. Minor *BCR-ABL* fusion gene was detected positive by qPCR. Based on these results, this patient was diagnosed as Ph^+MPAL. He also had a medical history of hypertension and type 2 diabetes mellitus for more than 5 years, which makes him not suitable for transplantation.

He received an induction chemotherapy (IA + CVP), which was idarubicin (I) 20 mg at d1, 10 mg at d2–3, cytarabine (A) 200 mg/d at d1–6, cyclophosphamide (C) 0.6 g at d1,8, vindesine (V) 4 mg at d1,8 and dexamethasone (P)10 mg/d. On day 5, imatinib (400 mg/d) was initiated in addition to the induction chemotherapy. On day 17, bone marrow biopsy showed that blast cell ratio was 41.5%. He continued the induction chemotherapy with imatinib (400 mg/d) and VP (vindesine 4 mg at d18,25 and dexamethasone 10 mg/d). The patient achieved hematological complete remission (CR) on day 37. Chromosomal analysis of bone marrow cells was (46, XY). Minor *BCR-ABL* fusion gene was negative. He received lumbar puncture and prophylactic intrathecal chemotherapy (methotrexate 10 mg + dexamethasone 5 mg). Subsequently, he continued to receive intensive consolidation therapy with imatinib (400 mg/d) plus IA + CVP, the same regimen as the first chemotherapy cycle. After the consolidation cycle, he developed severe pneumonia with suspected infection of Pneumocystis Jirovecii probably due to immunodeficiency. With the use of sulfaquinoxaline and mechanical ventilation in the intensive care unit, he recovered from the respiratory failure. Then he was given a reduced intensive consolidation therapy with imatinib (400 mg/d) plus IA + VP, methotrexate + CVAP, VAP, IA + teniposide, VAP + teniposide and CVAP + teniposide for another 6 cycles. During these consolidation cycles, he received lumbar puncture and prophylactic intrathecal chemotherapy repeatedly. Cerebrospinal fluid test showed elevated levels of protein without detectable leukemia cells. He did not receive allogeneic hematopoietic stem cell transplantation (allo-HSCT) because no suitable donor was found.

He achieved hematological, cytogenetic, and molecular CR until April 2013, when the bone marrow examination showed hypercellularity with 10% blasts. Chromosomal analysis of bone marrow cells showed (46, XY). Minor *BCR-ABL* fusion gene was 7.167%, detected by means of qPCR, but *ABL* mutation was negative, detected by next generation sequence. Since the patient relapsed within 1 month after consolidation therapy and he was in feeble condition caused by previous pneumonia, we decided to change the induction therapy to the combination of nilotinib (400 mg, bid) and lenalidomide (25 mg, qod) continuously. On day 35, he achieved hematological CR with good toleration. The nilotinib and lenalidomide were administrated to this patient without obvious side effect. The patient has complete hematological, cytogenetic, and molecular remission for 55 months until now. Written informed consent was signed by the patient and this study is approved by Ningbo First Hospital Ethic Committee.

3. Discussion

MPAL has been considered as a negative prognostic factor for the acute leukemia patients.[3] The presence of Philadelphia chromosome in MPAL leads to worse prognosis.[2] Imatinib, as a specific *BCR-ABL* tyrosine kinase inhibitor, has shown high efficacy in the CML treatment. Imatinib is also highly active in the Ph^+ALL treatment.[4] Thus, it is reasonable to add imatinib into the treatment of Ph^+MPAL. However, the responses of most Ph^+MPAL patients to imatinib were followed by the resistance and leukemia progression. For instance, Wang et al[5] reported that all of 12 Ph^+MPAL patients with chemotherapy plus imatinib without allo-HSCT, died within 3 years after diagnosis. Therefore, allo-HSCT has been long recognized as the only potential curative option for patients with Ph^+MPAL regardless incorporation of the TKIs (tyrosine kinase inhibitors).[3,5] However, the treatment strategy has not been established yet for patients who are ineligible for allo-HSCT due to age, lack of proper donors, or other reasons. Nilotinib and Dastinib are second-generation BCR-ABL inhibitors, which are more potent and selective than their first-generation counterpart, leading to superior outcomes in Philadelphia chromosome-positive malignancies.[6,7] For the patient in this case, though the *ABL* mutation was not detected at the relapse on April 2013, we replaced imatinib with nilotinib based therapy.

Lenalidomide is an oral immunomodulatory drug derived from thalidomide. This drug has been approved by the Food and Drug

Administration in the United States for treating lower risk myelodysplastic syndromes (MDS) with 5q deletion, multiple myeloma, and mantle cell lymphoma.[8] Clinical trials have been conducted for lenalidomide alone[9] or combination with other agents such as azacitidine,[10] bortezomid,[11] and cytalarbine[12] for higher risk MDS and acute myeloid leukemia (AML). Among these studies, the most remarkable combination was the sequential use of azacitidine plus lenalidomide for elderly AML patients, resulting in a CR or CR with incomplete recovery of blood counts (CRi) rate above 40%.[10] Moreover, a regimen with combination of azacitidine and lenalidomide has been successfully used as a bridge to allo-HSCT for relapsed/refractory AML patients.[13] However, the exact mechanisms of lenalidomide on AML have not been fully understood. Possible explanations for the efficacy of lenalidomide may include the inhibition of pro-inflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and IL-12, which play important roles in the pathogenesis of hematological malignancies.[14] In the meantime, lenalidomide has been reported to exhibit antiangiogenic activity through reducing vascular endothelial growth factor and fibroblastic growth factor production by the endothelium and bone marrow stroma.[15] In addition, lenalidomide can promote antitumor response by activating T cells and natural killer cells, inhibiting regulatory T cells and enhancing IL-2 and interferon-gamma production.[15] As a result, lenalidomide now is used for the treatment of AML. Furthermore, several studies have shown that a better response could be achieved in AML patients with lower peripheral or bone marrow blast counts following treatment of lenalidomide,[9,10] which may provide evidence for our treatment strategy. In our case, we prescribed lenalidomide to the Ph^+MPAL patient whose bone marrow harbored only 10% blasts at the relapse.

To our knowledge, this is the first case report describing a successful treatment strategy with maintenance chemotherapy in combination with nilotinib and lenalidomide for a Ph^+MPAL patient. Until now, this patient has achieved 55 months of CR without any conventional chemotherapy or allo-HSCT. In conclusion, combined TKIs with lenalidomide may represent an effective maintenance treatment regimen for Ph^+ MPAL patients who are not suitable for intensive treatments.

Author contributions

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