Case Report

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Chidamide combined with ibrutinib improved the prognosis of primary bone marrow diffuse large B cell lymphoma

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Abstract

Primary bone marrow diffuse large B cell lymphoma (DLBCL) is an independent pathologic type with a poor prognosis when treated with standard chemoimmunotherapy. Generally, rituximab-based high-dose chemotherapy regimens such as dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) can be administered to young patients, followed by autologous stem cell transplantation. For elderly patients, the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) regimen is well tolerated, but it is an insufficient induction therapy for this group. Herein, we reported an elderly patient diagnosed with primary bone marrow DLBCL, germinal center B-cell-like subtype. Considering tolerance, the R-CHOP regimen was administered. However, his disease progressed after two treatment cycles. Then, the rituximab, gemcitabine, dexamethasone, cisplatin, lenalidomide regimen was administered, but the patient still experienced disease progression. Subsequently, the histone deacetylase (HDAC) inhibitor chidamide and Bruton's tyrosine kinase (BTK) inhibitor ibrutinib were concurrently administered, and the patient achieved complete remission. We found that the response of primary bone marrow DLBCL to chemotherapy was poorer than that of de novo DLBCL. High-dose chemotherapy regimens such as DA-EPOCH should be administered to young patients in combination with rituximab. For elderly patients, new targeted drugs such as HDAC and BTK inhibitors appear to produce favorable outcomes.

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Keywords
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Introduction

Primary bone marrow diffuse large B cell lymphoma (DLBCL) is a rare, distinct, and aggressive lymphoma with poor prognosis that only involves bone marrow.[1] To date, few cases of primary bone marrow DLBCL have been described, and some cases occurred in elderly patients. It has been reported that young patients could achieve good prognosis following high-dose chemotherapy and stem cell transplantation. However, no recommended treatment strategy exists for elderly patients. In this study, we reported the case of an elderly patient with primary bone marrow DLBCL.

Case Report

A 65-year-old man complained of persistent pain in his right leg with no B symptoms for 6 months. On physical examination, no splenomegaly or peripheral lymphadenopathy was noted. Peripheral blood tests revealed pancytopenia and an elevated lactate dehydrogenase level (>1200 U/L). Superficial lymphadenopathy and hepatosplenomegaly were not observed via ultrasound. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography revealed increased FDG uptake in the medullary cavities of the bilateral humeri and femurs with a standardized uptake value of 12.3, suggestive of multiple myeloma (Figure 1). However, the immunofixation of serum and urine revealed no M protein. Analysis of his bone marrow aspirate disclosed increased numbers of large atypical B lymphoid cells that were positive for CD10, CD20, and PAX-5 and negative for CD34, CD38, CD138, CD56, CD3, TdT, MPO, and MUM1. The Ki-67 index for the lymphoid cells was 30%, which was not high (Figure 2). Flow cytometry revealed a monotypic population of B-cells (9.02%) that were positive for CD19, CD20, CD10, CD38, and surface kappa light chain and negative for CD3, CD4, CD5, CD7, CD8, CD13, CD33, CD34, and CD117. Cytogenetic studies identified a normal karyotype with 46, XY. Fluorescence in situ hybridization indicated negativity for IGH/CCND1, IGH/BCL2, TP53/CEP17, IgD, IgE, and MYC. Sequencing studies identified the L265P mutation in the MYD88 gene. A diagnosis of primary bone marrow DLBCL, germinal center B-cell-like subtype was made, and the international prognostic index and Ann Arbor stage were 4 and IV, respectively, portending a poor prognosis. After two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy, the patient's disease progressed. Then, the rituximab, gemcitabine, dexamethasone, cisplatin, and lenalidomide (R^2-GDP) regimen was administered, but disease progression was not slowed. Because of his fatigue, he could not tolerate further chemotherapy. Thus, the histone deacetylase (HDAC) inhibitor chidamide (20 mg biw) and Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (560 mg qd) were administered. Two months later, his

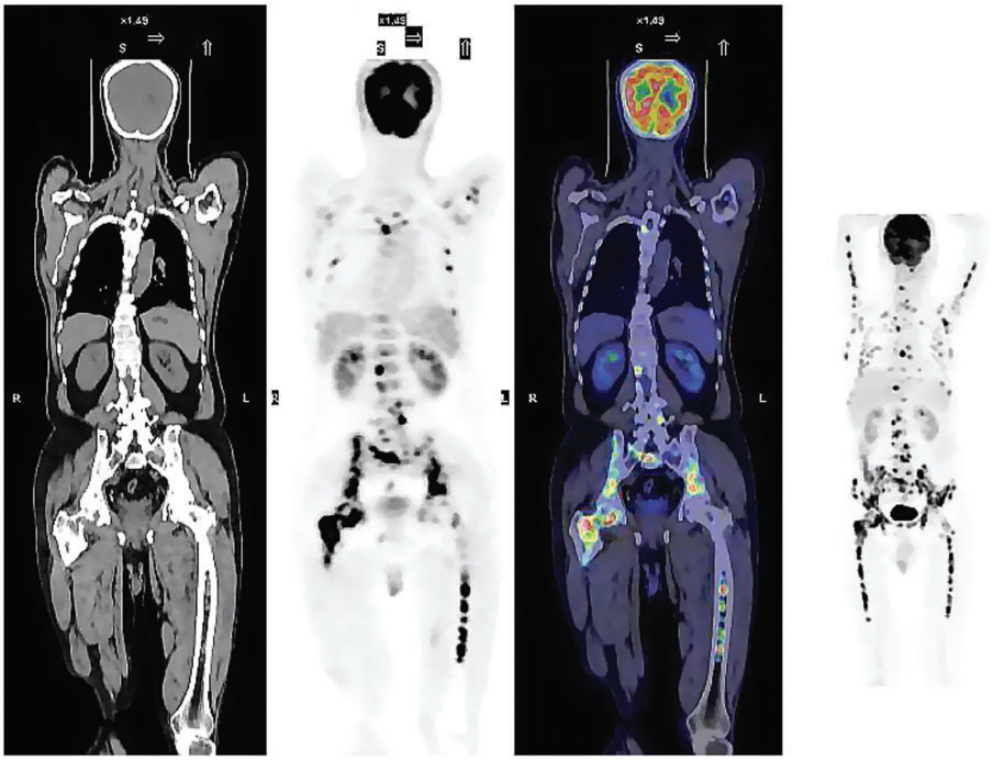

Figure 1. Positron emission tomography-computed tomography of the patient.

peripheral blood test result was normal, and the proportion of malignant cells in bone marrow had decreased to less than 5%, indicating complete remission (CR). The patient has received 18 cycles of chidamide and ibrutinib to date. His main adverse reactions were myelosuppression, nausea, vomiting, and fatigue, none of which was severe ($\leq$grade 2). By decreasing the chidamide dose from 20 to 15 mg biw, his discomfort was obviously improved. Although leukopenia developed during treatment, his tolerance was extremely good, and the patient has remained in remission to date. The patient's current progression-free survival is 18 months.

The study protocol was approved by the institute's committee on human research. The patient has given his written informed consent to participate to the study and for publication of this case report.

Discussion

Malignant lymphoma with bone marrow involvement is common. However, lymphoma originating from bone marrow without lymph node, spleen, liver, or other extra marrow organ involvement, also known as primary bone marrow lymphoma, is relatively rare. Bone marrow biopsy is critical for diagnosis. Primary bone marrow lymphoma can occur in various pathological types of lymphoma, the most common of which is DLBCL. Other types include Hodgkin's lymphoma, peripheral T cell lymphoma not otherwise specified, ALK-negative anaplastic large cell lymphoma, and follicular lymphoma.[2]

Because of its low incidence, there is no standard treatment for primary bone marrow DLBCL, especially for elderly

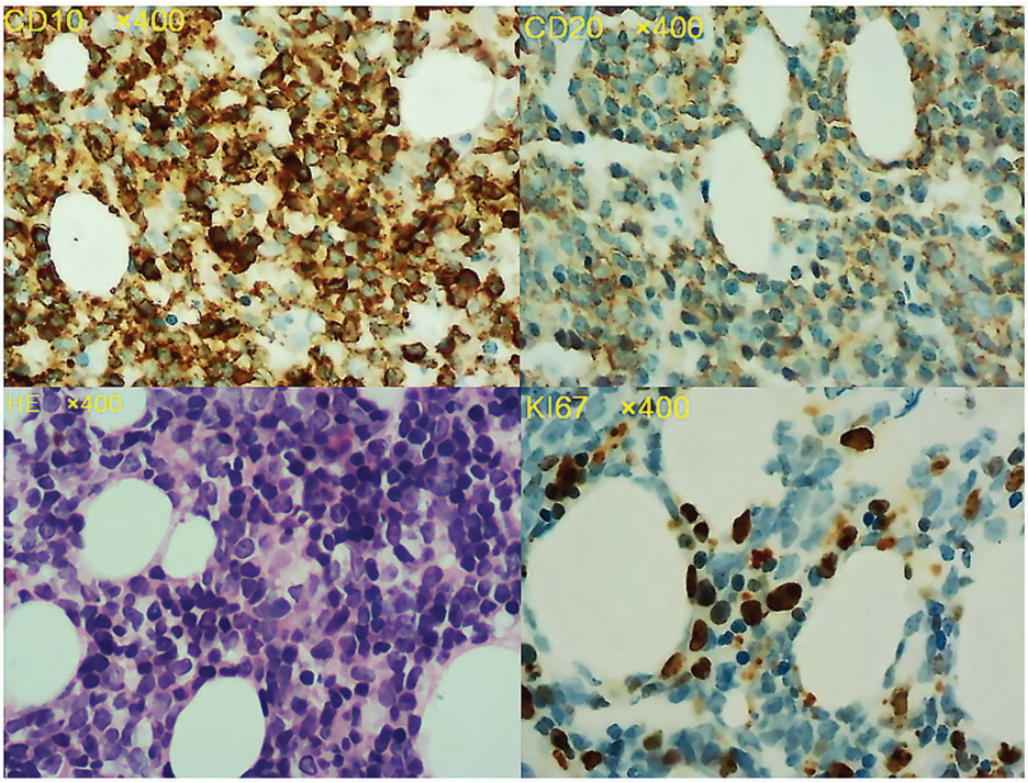

Figure 2. Immunostaining of bone marrow aspirate revealed CD10 and CD20 positivity. HE, hematoxylin and eosin.

patients.[3] Chang et al.[1] reported that rituximab combined with high-dose chemotherapy may improve the prognosis of patients with primary bone marrow DLBCL. For elderly patients, the R-CHOP regimen appeared to be a well-tolerated front-line treatment. However, its efficacy is not good, as observed in the present case, suggesting it is imperative to explore newer therapeutic options.

Many novel drugs are being investigated in elderly patients with DLBCL, either as monotherapy or in combination with chemotherapy. Among these new drugs, immunomodulating agents such as lenalidomide have produced good responses when combined with R-CHOP.[4] Mondello et al.[5] reported that lenalidomide monotherapy is effective against extranodal DLBCL with monoclonal gammopathy. However, in a large randomized phase 3 study, the addition of lenalidomide to R-CHOP failed to produce a survival advantage.[6] Mondello et al.[7] also reported that bendamustine and rituximab proved to be an efficacious and safe salvage therapy in an elderly patient with primary DLBCL of the bone. Because bendamustine is not available in China, the second-line regimen R^2-GDP was administered to our patient, but disease progression was not halted.

It has been reported that in activated B cell-like (ABC) DLBCL, NF-κB is typically dysregulated because of activation of the BCR signaling pathway. Selective targeting of BTK, which is a key tyrosine kinase of

the BCR pathway, has been demonstrated to inhibit NF-κB activation. Ibrutinib, a selective BTK inhibitor, displayed promising clinical activity in patients with relapsed ABC DLBCL.[8] In a trial involving 80 patients with relapsed or refractory DLBCL, ibrutinib produced a response rate of 37%.[9] Recently, it was reported that HDAC inhibitors could enhance the efficacy of ibrutinib against DLBCL.[10]

Chidamide, an innovative new drug independently developed in China, is designed to selectively inhibit the activity of HDAC1, HDAC2, HDAC3, and HDAC10 following oral administration. It was reported that selective inhibition of HDAC3 could activate immune surveillance in lymphoma, resulting in the inhibition of lymphoma cell growth.[11] A clinical trial assessing the efficacy and safety of chidamide in patients with DLBCL in mainland China is currently underway.

Conclusion

After concurrent treatment with ibrutinib and chidamide, the current patient achieved CR, indicating that the combination of HDAC and BTK inhibitors could improve the prognosis of primary bone marrow DLBCL, especially in elderly patients.

Authors' contributions

C.T. drafted and critically revised the paper. Y.L. and Z.C. revised the paper. All authors approved all versions including the final version, and all authors hold responsibility for the accuracy and integrity of all aspects of the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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