Case report

**Bendamustine Combined with Rituximab in the Treatment of Leukemic Non-Nodal Mantle Cell Lymphoma with Multiple Gene Mutations**

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**Abstract**

**Introduction:** Leukemic, non-nodal mantle cell lymphoma (MCL) is a relatively indolent disease characterized by asymptomatic leukemic presentation, non-nodal disease distribution, and slow disease progression, particularly in comparison to that of classic nodal MCL. TP53 and ATM deletions suggested poor prognosis. Here we reported a patient with many gene alterations showing a relative good response after BR therapy.

**Case report:** A 65-year-old woman presented with progressive fatigue for 3 months. Bone marrow aspiration and trephine biopsy revealed leukemic non-nodal mantle cell lymphoma (MCL). After two cycles of a regimen consisting of Bendamustine and rituximab, she achieved complete remission (CR).

**Conclusion:** It is generally believed that TP53 and ATM deletions suggested poor prognosis in MCL. Because of the severe anemia, the patient was treated with Bendamustine and rituximab and showed good response.

**Keywords:** Leukemic Non-Nodal Mantle Cell Lymphoma, TP53 Mutation, ATM Mutation, Bendamustine, Rituximab

**Introduction**

Leukemic non-nodal MCL is a relatively indolent disease characterized by asymptomatic leukemic presentation, non-nodal disease distribution, and slow disease progression [1-3]. Cytogenetic heterogeneity with TP53 and ATM deletions suggested a relatively aggressive clinical course [4,5]. Here we reported a patient with many gene alterations such as TP53, ATM, FAT1, EZH2, P21, PRDM1, CARD11 showing a relative good response to BR regimen.

**Case Report**

A 65-year-old woman complained of progressive fatigue for the past 3 months was administrated in our hospital. Physical examination revealed mild splenomegaly without hepatomegaly or lymphadenopathy. Laboratory test revealed anemia, with hemoglobin (Hb) of 5.5 mg/dL. Lactate dehydrogenases (LDH) were normal. Ultrasonic B and CT scan of the chest, abdomen, and pelvis were unremarkable except splenomegaly. Bone marrow aspiration and trephine biopsy revealed leukemic non-nodal mantle cell lymphoma (MCL). The lymphoma cells were positive for CD20, CD5, cyclin D1, and P53 and negative for CD3, CD43, and SOX11 with low Ki67 index (10%). Cytogenetic studies revealed a complex karyotype, as follows: 44, XX, -8, t(11;14) (q13;q32), -13, -17, +mar[11]/46, XX [3]. FISH studies confirmed the presence of IGH/CCND1. Next generation sequencing revealed mutations in TP53, ATM, FAT1, EZH2, P21, PRDM1, CARD11. The patient was diagnosed as leukemic non-nodal MCL with multiple gene mutations, suggesting poor prognosis. Treatment was initiated with rituximab (375 mg/m^2^ on day 1) and Bendamustine (90 mg/m^2^ on days 1 and 2) for six cycles. After 2 cycles of therapy her symptoms improved with blood counts almost normalized. Ultrasonic B showed reduction of spleen size and bone marrow biopsy showed normal trilineage hematopoiesis without evidence of MCL. The patient is currently receiving maintenance therapy with rituximab every 3 months that will be given for a total of 2 years.
Discussion

Mantle cell lymphoma (MCL) is a well-defined subtype of B-cell lymphoma characterized by t(11;14)(q13;q32)-driven overexpression of cyclin D1. Initially, leukemic involvement by MCL was thought to be associated with an aggressive clinical course and poor prognosis. However, a growing body of literature supports that MCL may involve peripheral blood and marrow in isolation and in the absence of aggressive nodal or non-nodal disease, and that these cases have an indolent clinical course and prolonged survival even without therapy [6,7]. According to 2016 World Health Organization (WHO) classification, MCL is divided into two subtypes: leukemic non-nodal MCL and classical MCL. Leukemic non-nodal MCL is a particular subtype of MCL, characterized by leukemic non-nodal disease and slow progression. Recognition of this entity is relevant to avoid overtreatment.

Although numerous genetic abnormalities are involved in the pathophysiology of MCL [8-10], not all are of prognostic value. TheCDKN2A locus (9p21), which encodes for both the CDK4/6 inhibitor INK4a (p16) and the positive TP53 regulator ARF (p14), is one of the most frequently deleted and is consistently associated with a poor prognosis in MCL. TP53 mutations or deletions are identified in 15% to 20% of MCL and are poor prognostic indicators. Leukemic non-nodal MCL with TP53, ATM and/or 13q14 deletions were reported to progress relatively quickly requiring initiation of therapy within an average of 16 months after initial presentation. Based on the aggressive nature and poor prognosis, these patients are usually treated at initial diagnosis with aggressive chemotherapeutic regimens such as hyper cyclophosphamide, vincristine, doxorubicin (Adriamycin), dexamethasone (CVAD).

The case we reported was an old woman diagnosed as leukemic non-nodal MCL with TP53, ATM, FAT1, EZH2, P21, PRDM1, CARD11 mutations. She was weak with severe anemia at diagnosis, so R2 regimen was given to her. Her response was good and received complete remission (CR) after two cycles. At present, she has remained in the CR stage for 2 years.

Compliance with Ethical Standards

The study was funded by grants 81670104 from the National Natural Science Foundation of China (NSFC).

Informed consent

Informed consent was obtained from the patient for being included in this case report.

Authors’ Contributions

Y.Y. drafted the paper. L.Z. and Z.C. acquired and analyzed the data. C.T. and Y.Z. critically revised the paper. All authors approved all versions including the final version and are responsible for the accuracy and integrity of all aspects of the manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest.

References