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Long-Term Remission in an Elderly Patient With Mantle Cell Leukemia Treated With Low-Dose Cyclophosphamide

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We present an elderly patient with mantle cell leukemia who was successfully treated with low-dose cyclophosphamide (CY). A 76-year-old female was diagnosed as mantle cell leukemia based on abnormal lymphocytosis and splenomegaly without lymphadenopathy. She was orally treated with 50 mg of CY daily and had continuous remission over 4 years. Rearrangements of BCL1 and immunoglobulin heavy chain genes in the peripheral blood lymphocytes were detected at diagnosis, but not 1 or 4 years later. Further studies are required to confirm the role of low-dose CY therapy for patients with mantle cell leukemia and lymphoma. Am. J. Hematol. 63:35–37, 2000.

Key words: mantle cell lymphoma; mantle cell leukemia; BCL1 gene; cyclophosphamide; continuous therapy

INTRODUCTION

Mantle cell lymphoma (MCL) is a distinct clinicopathological entity composed of small or intermediate cells with cleaved nuclei expressing B-cell associated antigens [1–3]. A common biological abnormality for MCL is the chromosome translocation t(11;14), resulting in rearrangement of the BCL1 gene and overexpression of cyclin D1 [3,4]. Although clinical and pathological aspects have been well characterized, the best treatment of MCL remains to be determined. Analogous to low-grade lymphoma, MCL occurs in elderly patients with generally asymptomatic advanced-stage disease, and patients with MCL are rarely cured with currently available therapy. However, in contrast to other indolent lymphomas, in which the median survival of advanced-stage patients is greater than 8 years, the median survival for patients with MCL is significantly shorter, with a range of 3–4 years [3,5]. Despite combination chemotherapy including anthracycline, no greater survival has been documented in the vast majority of patients with MCL [6].

The t(11;14)(q13;q32) is highly associated with MCL but is not restricted to this disease. A few patients with B-cell chronic lymphocytic leukemia (CLL) have been reported to have t(11;14). Recently, Neilson et al. [7] proposed the term "mantle cell leukemia" for B-cell CLL with t(11;14) presenting lymphocytosis without lymphadenopathy. Mantle cell leukemia shows an immunophenotype with positivity for CD5 antigen together with high levels of immunoglobulin (Ig) expression and weak or absent CD23 antigen, which are consistent with MCL rather than B-cell CLL. In contrast, it is likely that the t(11;14) is consistently absent in "true" B-cell CLL expressing CD5 and CD23 antigens as well as low levels of Ig. In this report, we present an elderly patient with mantle cell leukemia who achieved long-term remission by low-dose cyclophosphamide (CY).

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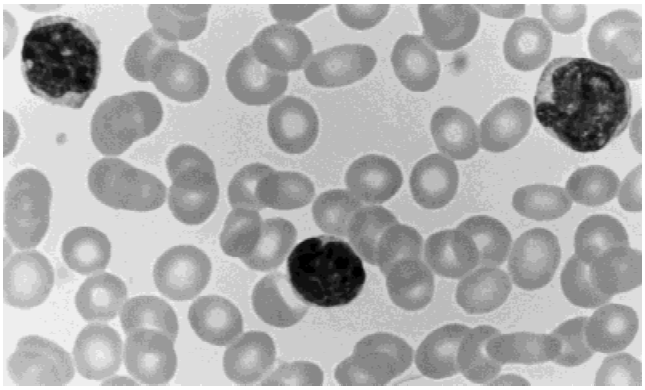

Fig. 1. Abnormal lymphocytes with an irregular nucleus in the peripheral blood (May-Giemsa staining).

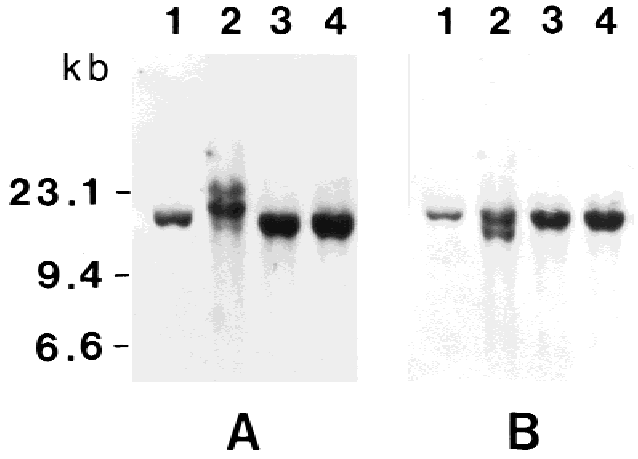

Fig. 2. Southern blot analysis of the immunoglobulin heavy chain (A) and BCL1 (B) genes. *Bam*HI-digested DNA samples were hybridized with the JH probe (C76R51A), and the filter was reprobed with the BCL1 fragment (pRH11). Lane 1, HL60 cell DNA serves as a control for the germline configuration; lane 2, the patient's DNA from the peripheral blood mononuclear cells at initial diagnosis; lanes 3 and 4, the patient's DNA from the peripheral blood mononuclear cells 1 and 4 years after the initiation of therapy, respectively. The rearranged BCL1 band did not comigrate with the rearranged JH band.

CASE REPORT

A 76-year-old otherwise asymptomatic Japanese female was referred to our hospital in March 1994 because of an 11-month history of lymphocytosis. Physical examination showed hepatomegaly 2 cm and splenomegaly 5 cm below the costal margin. No surface lymphadenopathy was found. The hemoglobin level was 11.5 g/dl, and the platelet count was 119×10^9/l. Her leukocyte count was 17.1×10^9/l with a differential of 10% neutrophils, 29% lymphocytes, and 61% abnormal lymphocytes. The bone marrow (BM) aspirate was normocellular with 50.8% lymphocytes. Blood chemistry showed normal results including serum LDH. Serum β_2-microglobulin was slightly elevated to 2.86 mg/l. Computerized tomography scanning revealed no mediastinal or mesenteric lymph node swelling. Abnormal lymphocytes in peripheral blood (PB) were of a medium size with irregular nuclei (Fig. 1) and were positive for HLA-DR, CD19, CD20, CD5 antigens, and μ and κ chains of Ig but not for CD10, CD2, CD3, CD23, CD25, or CD56 antigens. Although BM cells showed normal karyotypes on diagnosis, we found rearrangement of the BCL1 gene as well as Ig heavy chain (IgH) gene in PB mononuclear cells (Fig. 2). A diagnosis of leukemic phase of MCL (mantle cell leukemia) was made based on the above findings. Patient gave informed and written consent according to the guidelines by the Institutional Committee for the Protection of Human Subjects. Oral administration of 50 mg of CY per day was initiated. One month later, her leukocyte count decreased and the spleen was reduced in size. Seven months later, the leukocyte count was 3.0×10^9/l with 20% lymphocytes. No abnormal cells in the PB or BM were found, and the patient showed no splenomegaly, indicating complete remission. Nine months later, she received 50 mg of CY 3–5 times per week and the leukocyte count ranged between 2.5 and 3.5×10^9/l. The patient has continued remission over 4 years without any symptoms. No any adverse effect of the CY therapy has been observed. We found germline configurations of the BCL1 and IgH genes in the PB mononuclear cells 1 and 4 years after the initiation of therapy (Fig. 2).

DISCUSSION

MCL is now considered to be an aggressive lymphoma and is deemed incurable with currently available treatment [3,7,8]. High-dose chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation may improve the outcome of this disease [9]. Since MCL occurs in elderly patients with a median age 63–65 years [6,8], this approach can be applied to a relatively small proportion of MCL cases, while the need to develop alternative less aggressive therapies for the majority of patients not suitable for high-dose therapy is underscored. We here present a case of mantle cell leukemia successfully treated with low-dose CY. Although this result is not equivalent to true molecular remission because of limitation of sensitivity in Southern blot analysis, it is noteworthy that the patient has continued long-term remission with less aggressive therapy. Whether mantle cell leukemia has a poor prognosis similar to that of MCL is yet unclear. Dascalescu et al. [10] have reported a poor prognosis of their three cases of mantle cell leukemia with survival of 21, 26, and 72 months. It is also demonstrated that PB involvement is one of poor prognostic factors of MCL in multivariate analyses [6]. It is necessary to confirm the putative benefit of low-dose

CY therapy in large numbers of mantle cell leukemia and MCL patients.

The reason for the effectiveness of low-dose CY therapy against this refractory disease is not known. A most salient feature of low-dose CY compared to other current therapies is continuous drug administration. Hiddemann et al. [11] observed that response to chemotherapy in patients with MCL occurs later and at a slower pace than that in patients with follicle-center lymphoma, and they suggested that prolonged rather than intensive cytoreductive treatment may facilitate an increased rate of remissions. The current low-dose CY therapy shares such a prolonged low-intensity treatment feature. Long-term remission in our patient may be associated with continuous therapy which controlled the leukocyte count at a low level. Whether low-dose CY therapy is effective for MCL patients showing a high LDH level is unclear. Since the initial response rate of MCL to conventional therapy is similar to that in other low-grade or intermediate-/high-grade lymphomas, low-dose CY therapy may be offered for post-remission therapy to improve disease-free survival, particularly in elderly patients.

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