Long-term cytogenetic remission with ubenimex monotherapy in a case of chronic myeloid leukemia

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A 65-year-old man was diagnosed with chronic myeloid leukemia (CML) in February 1990, and was treated with busulfan and ubenimex. Cytogenetic analysis of the bone marrow revealed the Philadelphia (Ph) chromosome in 100% of cells of analyzed at diagnosis. Treatment with busulfan was stopped in March 1993 due to bone marrow suppression. The Ph chromosome was seen in 80% of cells in June 1993. He received ubenimex monotherapy after cessation of busulfan. Complete disappearance of the Ph chromosome was confirmed in May 1995 and has continued to date. This suggests that ubenimex might specifically affect the Ph chromosome and be useful as maintenance therapy for CML. ***Anti-Cancer Drugs*** **15:729–731 © 2004 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2004, **15**:729–731

Keywords: chronic myeloid leukemia, complete cytogenetic response, ubenimex

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Received 3 March 2004 **Accepted** 18 April 2004

Introduction

Chronic myeloid leukemia (CML) is a clonal disorder with a reciprocal t(9;22)(q34;q11) chromosomal translocation known as the Philadelphia (Ph) chromosome [1]. The newly introduced tyrosine kinase inhibitor, imatinib mesylate, has been demonstrated to be effective for CML [2]. However, the long-term outcome for the patients with CML treated with imatinib alone is unknown. It has been reported that an aminopeptidase inhibitor, ubenimex (Bestatin; Nippon Kayaku), is also useful for treatment of CML [3]. We describe here a case of a patient with CML who has shown long-term cytogenetic remission with ubenimex monotherapy following busulfan treatment.

Case report

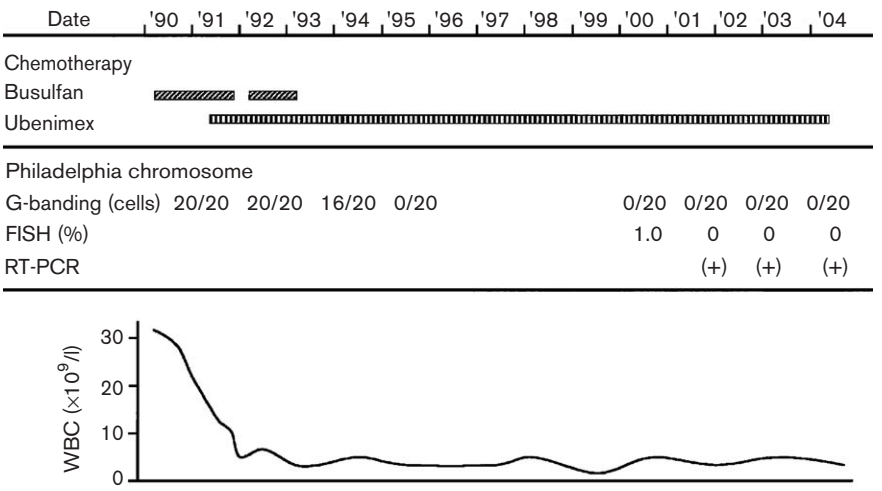
A 65-year-old man was admitted to our hospital in January 1990 because of leukocytosis. Physical examination at admission revealed splenomegaly, but no lymphadenopathy. The peripheral blood examination indicated a white blood cell count of 35.7×10^9/l with 0.5% blasts, 1.0% promyelocytes, 1.0% myelocytes, 3.0% metamyelocytes, 67.0% neutrophils, 1.0% eosinophils, 10.5% basophils, 2.0% monocytes, 14.0% lymphocytes, hemoglobin concentration of 12.7 g/dl and a platelet count of 469×10^9/l. The results of serum biochemical and serological tests showed increased serum levels of lactate dehydrogenase and vitamin B_{12}. Bone marrow aspirate showed hypercellular marrow with 2.5% myeloblasts. Cytogenetic study of bone marrow cells indicated an abnormal karyotype of 46, XY, t(9;22)(q34;q11) in all of the 20 cells analyzed. He was diagnosed as having CML in the chronic phase and received busulfan at a dose of 2 mg/day from February 1990. Then, he received an additional therapy with ubenimex at a dose of 30 mg/day from March 1991 (Fig. 1). After 2 years of chemotherapy, white blood cell count decreased to 4.4×10^9/l and platelet count to 110×10^9/l. He had no symptoms and obtained a hematologic remission. Busulfan was stopped in May 1993 because of myelosuppression and he was then treated with ubenimex alone for CML. Cytogenetic study revealed the Ph chromosome in 16 of 20 cells in June 1993. Adverse events caused by ubenimex did not occur during treatment. The durable remission in the peripheral blood examination has been seen more than 10 years after cessation of busulfan. Complete disappearance of Ph chromosome in the bone marrow was confirmed in May 1995. In addition, Ph chromosome could not be detected by fluorescence *in situ* hybridization (FISH) for BCR/ABL in 2001. The cytogenetic complete response has continued for more than 8 years, but minimal residual disease has been still detected by RT-PCR for the major *BCR/ABL* mRNA transcript.

Discussion

The therapeutic strategy for patients with CML is undergoing substantial changes due to emerging evidence regarding the effectiveness of imatinib mesylate [4,5].

0959-4973 © 2004 Lippincott Williams & Wilkins DOI: 10.1097/01.cad.0000136880.34799.27

Fig. 1



Clinical course.

Despite the widespread use of imatinib in CML it is still uncertain whether this drug is effective in long-term disease control. Moreover, drug resistance sometimes occurs in the blast phase [6] and it is suggested that acquired resistance could be caused by mutations in the *BCR/ABL* kinase region [7].

Ubenimex, one of the aminopeptitase inhibitors, has been used for patients with acute myeloid leukemia, myelodysplastic syndrome (MDS) or CML in Japan [3,8,9]. In a previous report, ubenimex has been shown to prolong the survival of patients with acute myeloid leukemia as a biological response modifier [10]. However, it has also been described that ubenimex was not beneficial for patients with MDS and acute leukemia derived from MDS [9]. It is of interest that combination therapy with ubenimex and busulfan induced a cytogenetic response compared with busulfan alone in CML [3]. In our case, a complete cytogenetic response was obtained after discontinuation of busulfan treatment. Although we cannot completely exclude the synergic effect with busulfan, it has been shown from the minimal cytogenetic response to complete cytogenetic response during ubenimex monotherapy. Therefore, this phenomenon suggests that ubenimex might directly affect the Ph chromosome.

Recently, Sawafuji *et al.* have reported that ubenimex inhibits proliferation and induces apoptosis of both K562 cells (CML cell line) and imatinib-resistant K562 cells [11]. They have also demonstrated that phosphorylation of mitogen-activated protein kinase is suppressed in these cell lines with ubenimex treatment. In another experiment using long-term culture-initiating cells, it has been described that ubenimex selectively suppresses Ph^+ clones without affecting normal hematopoiesis in the bone marrow cells derived from CML patients [12]. Furthermore, Mishima *et al.* have found that the combination of imatinib and ubenimex had a synergic effect on the proliferation of CML cell lines [13].

Ubenimex was very effective in eliminating Ph chromosome without adverse events in our case. Complete cytogenetic response has been verified as reliable surrogate measures for long-term survival in patients treated with interferon-α [14]. In consideration of recent *in vitro* results, it might be possible that ubenimex is useful as an alternative therapy or in combination with imatinib for patients with CML in the chronic phase.

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