

## Long-lasting response of chronic lymphocytic leukemia and multiple sclerosis in a patient treated with oral fludarabine alone

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**To the Editor:** We report on a case in which fludarabine was given orally to a patient with chronic lymphocytic leukemia (CLL) and with a previous diagnosis of relapsing/remitting multiple sclerosis (MS).

In June 2003, a 55-year-old woman with a persistent peripheral blood lymphocytosis was diagnosed as having B-cell CLL. Previous medical history included a five-year history of relapsing/remitting MS. At diagnosis, a moderate spastic paraparesis and dysmetria (EDSS 3.5) were found. Magnetic resonance imaging revealed multiple demyelinating lesions on the brain and spinal cord. The patient was treated with oral prednisone with very poor results. In December 2000, she was treated with interferon (IFN) beta-1b 8,000,000 IU three times weekly. In December 2002, IFN was reduced to 8,000,000 IU two times weekly because of the appearance of a lymphocytosis (WBC 12,130/ $\mu$ l of which 5,095/ml were lymphocytes). At Hospital admission (June 2003), physical examination, abdominal ultrasound and thoracic X-ray revealed no node or abdominal organ enlargement. A complete blood cell count showed: hemoglobin 13.4 g/dl; WBC 10.370/ $\mu$ l, of which 5,185/ $\mu$ l were small and mature-appearing lymphocytes; platelet count 190x10<sup>9</sup>/l. Renal and hepatic function and coagulation tests were normal. Thirty percent of mature-appearing lymphocytes were detected in the bone marrow. Both peripheral and bone marrow lymphocytes had the following immunologic profile: CD19+ CD5+ CD23+ CD22+ low-density FMC7- CD79b- CD38-kappa light chain restriction with weak expression. On this basis, a diagnosis of B-cell CLL 0 (Rai)/A (Binet) clinical stage was made. No treatment was deemed necessary, and re-evaluations at 3-month intervals were recommended. In October 2003, the patient presented with bilateral cervical, submandibular and inguinal node enlargement. Complete blood cell count showed

WBC 13,800/ $\mu$ l, of which 8,418/ $\mu$ l were lymphocytes, normal hemoglobin level and platelet count. At the same time, a diagnosis of chronic epithelioid necrotizing granulomatosis was made by means of a histologic evaluation of samples obtained by surgical resection of the right lobe of the lung because of multiple nodular lesions. Since complete blood cell count showed stable values, no specific therapy was given. In June 2004, IFN beta-1b had to be stopped due to increased spasticity and worsening of the gait. In October 2004, a total body computed tomography showed abdominal and bilateral axillary and inguinal node enlargement. WBC was 13,000/ $\mu$ l, of which 7,800/ $\mu$ l were lymphocytes. Hemoglobin level and platelet count were again normal. Neurologic examination showed a gradual worsening of the MS, and once-a-week therapy with IFN beta-1a 6,000,000 MIU was initiated. In January 2005, the patient experienced fever and a sudden doubling of lymphocyte cell count (WBC 30,150/ml, of which 15,980/ml were lymphocytes, with normal hemoglobin levels and platelet count). Physical and ultrasound examination revealed an increase in peripheral and abdominal node size. Elevated lactate dehydrogenase levels were also found. To rule out Richter's transformation, a node biopsy was performed and showed cyto-architectural features consistent with a small lymphocytic lymphoma/CLL, according to the WHO classification. On this basis, IFN beta-1a was definitively stopped, and oral fludarabine was given at 40 mg/m<sup>2</sup> daily for 5 consecutive days. At the end of the fourth cycle (July 2005), a complete remission of CLL was documented (normal complete blood cell count, flow cytometrically undetectable clonal B-cells, and disappearance of node enlargement). The neurological examination showed an improvement of both asthenia and gait. In light of this, fludarabine therapy was stopped and the patient underwent a strict bi-monthly follow-up for both her neurological and hematological conditions. At the last follow-up (August 2008), a persistent hematologic complete response and a stable neurologic condition once again were found, and the patient remains therapy-free for both diseases.

Fludarabine monophosphate is a purine nucleoside analog with its major activity in indolent lymphoid malignancies. It currently represents the backbone of CLL therapy and acts by incorporation of the active 5'-triphosphate of fludarabine, F-ara-ATP, into RNA and as a very effective chain terminator in DNA synthesis<sup>1</sup>. High response rates have been reported in CLL treated only with fludarabine: approximately 80% overall response, 20-30% of which were complete remissions. By combining fludarabine with alkylating agents such as cyclophosphamide (Flu-Cy regimen), higher response

rates have been obtained due to the ability of fludarabine to inhibit excision repair of DNA interstrand cross links induced by cyclophosphamide<sup>2</sup>. Immunosuppression, with both CD4 and CD8 T-lymphocyte reduction, is generally observed after the first three cycles of treatment, and recovery to normal values is very low<sup>3</sup>. MS is now regarded as an immune-mediated disorder involving one or more antigens located in the myelin of the central nervous system<sup>4</sup>. Myelin-reactive T-cells lead to inflammatory demyelination<sup>5</sup>. Immunosuppressive agents, such as azathioprine, IFN, cyclophosphamide and, more recently, mitoxantrone, are currently used to treat MS, in particular in remittent forms. Finally, reports have been published on the use of the monoclonal antibodies rituximab and alemtuzumab.

Purine analogues, in particular 2-CdA, showed activity in autoimmune disorders and graft-versus-host disease (recently reviewed by Robak *et al.*)<sup>1</sup>. Fludarabine has been tested only in a clinical trial to treat rheumatoid arthritis<sup>6</sup>. Twenty-six patients with severe rheumatoid arthritis, refractory to previous therapy, were treated with 20 mg/m<sup>2</sup> or 30 mg/m<sup>2</sup> daily for 3 consecutive days given monthly for 6 months. Seventeen percent of patients treated with lower doses and 50% of patients in the higher dose group showed a good clinical response after 6 months of therapy, thus showing the potential efficacy of fludarabine also in the treatment of autoimmune disorders. This is also the basis for the use of high-dose therapy followed by stem cell rescue to accelerate myeloid recovery. MS is now the most common autoimmune disorder for which such a condition is performed<sup>7</sup>. To our knowledge, this is the first report on the efficacy of fludarabine in remittent/relapsing MS in a patient in

which the drug was used for a concomitant diagnosis of CLL. Our experience, although limited, supports the hypothesis that administering fludarabine to our patient had an immunosuppressive effect on MS, a disease now regarded as an autoimmune disorder.

## References

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