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# LETTERS AND CORRESPONDENCE

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## Fludarabine-Related Hemolytic Anemia in Chronic Lymphocytic Leukemia and Lymphoproliferative Disorders

*To the Editor:* Fludarabine, which is a potent inhibitor of adenosine deaminase, is an effective agent in the treatment of chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (NHL) [1]. One of its major side effects is a profound T-cell immunosuppression and autoimmune hemolytic anemia (AIHA) [2]. To investigate the incidence and any risk factors of development of AIHA, we conducted a retrospective study of 20 patients with advanced CLL and low-grade NHL resistant to treatment with alkylating agents, who were treated with fludarabine between 1994–1996.

Four patients with CLL and small cell cleaved NHL with a mean age of 64 years (range, 45–72 years) developed AIHA after treatment with fludarabine. All had stage C disease for the three cases of CLL, and stage III B for the case with NHL. Three patients had no previous history of hemolysis and a negative Coombs' test before the start of fludarabine treatment. One patient had a history of AIHA that was controlled with low-dose prednisone at the time of treatment with fludarabine and Coombs' test reverted to negative. All developed severe AIHA with positive Coombs' test after a median of four courses (range, 2–6 courses). All patients required treatment with prednisone and in some cases red cell transfusion. None of these patients had a recurrence of the hemolytic reaction after tapering of steroids but only one patient had a negative Coombs' test after treatment. None of these patients restarted on fludarabine after control of hemolysis.

The incidence of AIHA in patients treated with fludarabine was investigated by Di Raimondo et al. [3]. They found five patients without pre-existing AIHA and four patients with pre-existing AIHA who developed hemolysis after one to six courses of fludarabine among a group of 112 patients with CLL (8%); however, others reported a higher incidence (21%) [4]. In most cases, hemolysis occurs after a mean of four courses of fludarabine and tends to be severe and has an abrupt onset. Usually hemolysis can be controlled by prednisone at a dose of 1 mg/kg. In some cases it is possible to administer further courses of fludarabine safely. But, commonly, further courses of fludarabine lead to hemolytic exacerbation that is usually difficult to control. In our study, we have a patient with a pre-existing AIHA who developed hemolysis after only two courses of treatment, which is consistent with the possibility that patients with pre-existing AIHA are at a higher risk of developing this complication. It is recommended that such patients either receive other forms of treatment or receive fludarabine with prophylactic corticosteroids because patients receiving a combination of fludarabine and corticosteroids are at a higher risk of systemic infection. It is recommended that this treatment be given under both antifungal and antipneumocystis protection. The mechanism of fludarabine-related AIHA is not clear. It may be related to the tendency of fludarabine to produce profound and long-lasting T lymphopenia. Self-tolerance is believed to be maintained by the suppression of autoreactive T cells by autoregulatory T cells. It seems that fludarabine enhances the T-cell defect and greatly increases the risk of autoimmunity [5].

**HESHAM M. TAHA**
*Hematology/Oncology Fellow, New York Methodist Hospital, Brooklyn, New York*

**PARTHS NARASIHMAN**
*Chief of Hematology/Oncology, North Shore University Hospital, Forest Hill, New York*

**LATHA VENKATESH**
*Medical Resident, North Shore University Hospital, Forest Hill, New York*

**MARGRETE CAWLEY**
*Clinical Nurse Specialist, New York Hospital Medical Center of Queens, New York*

**BARRY KAPLAN**
*Chief of Hematology/Oncology, New York Hospital Medical Center of Queens, New York*

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## Prolymphocytic Transformation of B-Chronic Lymphocytic Leukemia Presenting as Malignant Ascites and Pleural Effusion

Prolymphocytic transformation is a complication of chronic lymphocytic leukemia (CLL) associated with increasing splenomegaly, leukocytosis