Case Report

Fludarabine Induced Autoimmune Haemolytic Anaemia in a Patient with Chronic Lymphocytic Leukaemia

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Abstract

Autoimmune haemolytic anaemia following fludarabine is an uncommon complication and previously treated patients are at higher risk.

We describe a case of 57- year old lady with chronic lymphocytic leukaemia; she received intermittent courses of alkylating agents and purine analogue, fludarabine. Reintroduction of fludarabine for her relapsing disease induced autoimmune haemolytic anaemia.

Numbers of cases have been reported regarding autoimmune haemolytic anaemia following fludarabine administration, but none have been published from our part of the world.

Normally T-cell suppresses autoreactive lymphocytes that can produce autoantibodies. Suppression of T-cells by fludarabine, in addition to the underlying disease process appears to be a contributory factor for autoimmune haemolytic anaemia.

Introduction

Autoimmune haemolytic anaemia (AIHA) is caused by autoantibodies against antigens on the surface of red blood cells.[1] The result in increased destruction and shortened life span of erythrocytes.[1]

Autoimmune phenomenon is a well known complication of lymphoproliferative disorders, particularly of chronic lymphocytic leukaemia (CLL).[2]

Fludarabine, a purine analogue was introduced as a new and potent therapy for chronic lymphocytic leukaemia in 1980[3] and since then, it is an effective and frequently used agent for refractory and relapsing disease.[4] Autoimmune disease, immunosuppression[5] and second neoplasm in patients affected by B-cell chronic lymphoproliferative disorder are well known complications after fludarabine therapy.[6]

Autoimmune haemolytic anaemia is a rare complication of fludarabine therapy. Not many cases have been reported in the literature, and none from Pakistan.

We report a case of autoimmune haemolytic anaemia following fludarabine in a patient with chronic lymphocytic lymphoma.

Case Report

A 57 year old female presented in July 1999, with complaints of fever and abdominal distension. General physical and systemic examination revealed hepatosplenomegaly. Complete blood counts showed: white cell count $102x10^9$/L with 88% lymphocytes, haemoglobin 8.9g/dl and platelets $106x10^9$/L. Bone marrow aspirate and trephine biopsy revealed diagnosis of chronic lymphocytic leukaemia. She had Ann Arbor stage IV disease and underwent splenectomy. Subsequently she was given six intermittent courses of chlorambucil to control her progressive disease. After that she remained well for about eight months.

Disease progression was seen again in December 2001, when her white blood cell count had risen to $99x10^9$/L. Patient was otherwise well with normal haemoglobin and platelets. Fludarabine monophosphate therapy was initiated at dose of $40mg/m^2$ for five days, repeated every four weeks. She received a total of nine courses over a period of one year and showed a reasonably good response.

Off therapy she remained well till January 2005, when she presented with progressively rising white cells count. Fludarabine was reintroduced at previous dose; $40mg/m^2$ for five days. At beginning of therapy complete blood counts were: white cell count $105x10^9$/L with 85% lymphocyte, haemoglobin 10.2gm/dl and platelets $51x10^9$/L and direct coombs test was negative. Two weeks later, she presented with generalized weakness, shortness of breath on minimal exertion and pallor. On physical examination, she had pallor, scleral icterus and tachycardia. Complete blood counts at that time revealed: haemoglobin 4.8gm/dl, Hct 12.6%, TLC $4.5x10^9$/L, platelet $41x10^9$/L, peripheral blood smear revealed spherocytes and nucleated red blood cells (Figure). Other laboratory workup was notable for reticulocyte count 26%, LDH 1064 IU/L, and indirect bilirubin 4.5mg/dl (0.6-1.5mg/dl). Direct coombs test was strongly positive with polyspecific anti IgG and anti-C3d.

The patient was started on oral prednisolone 1mg/kg/day and meanwhile transfused with least incompatible blood products. She showed marked and rapid

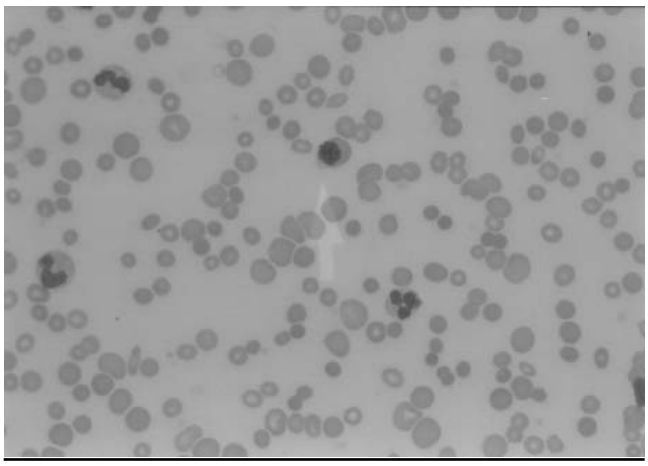

Figure. Peripheral Blood Film

improvement with resolution of her symptoms and increase in haemoglobin to 8.3gm/dl, Hct 24% and platelet 67,000/ul after a week. Direct coombs test became negative and reticulocyte count dropped to 11%. Prednisolone was gradually tapered off over two months. On recent follow-up on 13 June 2005, complete blood count revealed Hb 13.0g/dl, Hct 38%, TLC 5.6x10^9/L and platelets 291x10^9/L.

Discussion

Chronic lymphocytic leukaemia is a low grade B-cell lymphoproliferative disorder.[6] Splenectomy, splenic irradiation and alkylating agents are active therapies for the disease but recurrence is frequently observed.[6] During late 1980s, fludarabine emerged as a major drug in chronic lymphocytic leukaemia and generated tremendous interest.[7]

The incidence of autoimmune cytopenias in chronic lymphocytic leukaemia is significantly higher than in general population; autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura and pure red cell aplasia occur with incidence of 4-40%, 1-2% and less than 1% respectively.[1-3, 5, 8]

It is reported that patients with de-novo CLL treated for first time with fludarabine are unlikely to develop autoimmune haemolytic anemia.[8] Accumulated experiences of several centers suggested that the incidence of fludarabine induced AIHA in patients with CLL with or without positive DAT; ranges from 2% in previously untreated patients to more than 20% in heavily pretreated patients.[8]

In addition, it was observed that patients, who have been treated with multiple courses of alkylating agents, are at higher risk of developing AIHA following fludarabine therapy.[9]

Our patient was treated previously with alkylating agents multiple times followed by fludarabine. Re-exposure to fludarabine induced autoimmune haemolytic anaemia.

Although the etiology of autoimmune disease following purine analogue is unknown, but it appears to be multifactorial.[10]

The most notable side effect of fludarabine is profound and long lasting T-cell lymphocytopenia and alteration of CD4-CD8 cell ratio[10], these leads to loss of control of normal T-cells to autoreactive lymphocytes.

Raymond et al[10] described that imbalance in the CD4-CD8 ratio, is the best explanation for the development of AIHA in patients who responded to fludarabine therapy and this might be the reason in our patient as well.

As our patient is an elderly lady, declining thymic functions with advancing age and decreased T-cell function in CLL may also act as contributory factors.

So autoimmune haemolytic anaemia may have been due to fludarabine associated immunosuppression, underlying disease process, advancing age or combination of all.[7]

In summary, patient with chronic lymphocytic leukaemia are more prone to develop autoimmune haemolytic anaemia, especially when they are previously heavily treated. So haematologic vigilance and a high index of suspicion is essential throughout the period of fludarabine therapy especially in previously treated patients, because haemolysis can occur without warning and requires corticosteroid therapy promptly, which is the most effective therapy for autoimmune haemolytic anaemia.

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