Case Report

Fludrabine combined therapy(FCR) induced Evans syndrome in patient with Chronic Lymphocytic Leukemia after stopping therapy

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Autoimmune disorders frequently complicated chronic lymphocytic leukemia (CLL) such as autoimmune hemolytic anemia, immune thrombocytopenia, pure red cell aplasia and autoimmune granulocytopenia.
however ,Some drugs such as fludarabine and other purine analogue to some extent may increase the risk of these phenomena.. Physicians should be aware of the risk of severe AIHA in CLL patients previously treated with fludarabine administration .it has been reported patient with (CLL) may developed fatal intravascular autoimmune hemolytic anemia (AIHA) after treatment with fludarabine. Here, a case with CLL complicated with severe autoimmune hemolytic anemia and immune thrombocytopenia post treatment with fludarabine combined therapy after he finishing treatment cycles in patient with complete remission which is successfully re treated by rituximab .

Introduction

Chronic Lymphocytic Leukemia (CLL) therapy can induce autoimmune cytopenias, particularly autoimmune hemolytic anemia (AIHA). It is critical to diagnose cytopenias from these secondary complications of CLL accurately, since prognosis and therapy are substantially different from patients who have cytopenias due to extensive bone marrow infiltration by CLL

Unfortunately, the diagnosis of AIHA can be difficult to make in the setting of CLL because the laboratory values for hemolysis may be distorted in CLL due to disease progression or therapy.(1)

Single-agent purine analog therapy (such as fludarabine) is known to induce hemolytic anemia in CLL patients.(2,3)

Patients who have received multiple prior therapies appear to be at a higher risk for this complication.The exact mechanism by which fludarabine induces hemolysis is unclear, but it likely secondary to an alteration in the peripheral blood TH17/Treg ratio in these patients.(4)

Traditional therapy of autoimmune complications in CLL consists of immunosuppression with corticosteroids and/or anti-CD20 monoclonal antibodies. In patients who have a suboptimal response, treating the underlying CLL is generally effective in ameliorating secondary cytopenias.

Case Report

A 67 years old male diagnosed as having Binet stage C of chronic lymphocytic leukemia diagnosed in February 2017 with cervical, axillary, abdominal lymphadenopathy ,splenomegaly and constitutional symptoms.
His initial complete blood pictures showed :hemoglobin 13.9 g/dl,white blood cell 112X109 /l And platelet 103X109/l with absolute lymphoctyosis ,mainly mature looking lymphocyte.Coombs test was negative.
Bone marrow aspirate and biopsy :showed infiltration by abnormal lymphoid with diffuse infiltration on bone marrow biopsy
Flowcytomtery :lymphoid cell showed CD19 ,CD5,CD23,CD11c,CD20 were positive While lack of CD10,CD79a,FMC7,kappa @Lamda ,sIgG , CD25 ,CD103,CD123 with feature consistent with chronic lymphocytic leukemia
Abdominal ultrasound showed hepato splenic enlargement with Para aortic lymphadenopathy
He started therapy on March 2017 with chlorambucil and prednisolone intermittent therapy every 21 days for 12x cycles with improvement in his constitutional symptoms and regression liver and splenic size, despite his platelet dropping down (75X109/l). later on patient kept on observation till August 2018 where the patient started to have re enlargement of liver and spleen and new group of abdominal lymphadenopathy involving Para aortic and mesenteric group of lymphadenopathy
because of logistic purposes and un availability of bendamustin so patient started with Lite RFC(Rituximab,fludrabine,Cyclophosphamide) on November 2018 post FISH study for 17p Del which was negative .Patient received 6x cycles smoothly with improvement of platelet and normalization of organomegaly and abdominal lymphadenopathy. THe last cycle on June 2019 Patient attained Complete remission post 6X cycles according to CLL response criteria with
On December 2019 patient presented with fatigue , dyspnea and chest discomfort with no drug history or fever .physical examination revealed anemia, jaundice . At this time there is dropping of hemoglobin level and mild splenic enlargement with no peripheral lymphadenopathy . His hemoglobin level 5.5 g/dl with normochromic macrocytic ,tear drop cell with leukopenia ,lymphopenia and severely reduced platelet
CBC 5.5 g/dl WBC 3.4X10/l platelet 10X109 /l
coombs test was positive, corrected retic 5.7% ,ESR 150mm ,with increased indirect hyper bilirubinemia 4.8mg/dl ,direct bilirubin 0.43 mg/dl and normal liver function test ,high LDH
Bone marrow aspirate showed active erythropoiesis with some megaloblastic feature and erythroid hyperplasia which over shadow myelopoisis and normal megakaryocyte number with different maturation stage .Lymphocyte 15%,blast 1%.Biopsy showed focal infiltration by lymphoid cell with mature form and small aggregate of primitive cell of doubtful nature
Immune histochemical stain on bone marrow biopsy showed :CD34 negative,CD20 focally positive,CD3 positive for diffuse cells ,CD5 negative,CD23 negative, VWF positive for megakaryocyte ,so impression was cellular marrow with no definitive recurrence
Pan CT of neck, chest , abdomen and pelvic for possibility of Richter transformation were negative
The patient was hospitalized and he started on prednisolone with 1mg/kg ,folic acid and irradiated blood transfusion .One week later his complete blood picture does not showed much improvement with 6.4g/dl,WBC 2.9X109 /l And platelet 14X109 /l and increasing total serum bilirubin to 7mg/dl which is mainly indirect .

Three weeks later CBC showed still hemoglobin 6.3 gm/dl ,WBC 2.4X109/l and platelet 55X109/l with total bilirubin 2.2 mg/dl
Patient planned to started methylpredensolon 1g for three days with Rituximab (375 mg/m2)(as long as there is no evidence of underlying active disease). Hemoglobin started to raise to 8gm/dl two weeks later. Patient received weekly Rituximab for four doses to be followed after one month with another dose of Rituxmab with tapering prednisolone .Last CBC on February 2020 was 11.2 g/dl and platelet count 135X109 /l .

Discussion:

Secondary autoimmune cytopenias in the setting of CLL are primarily due to non-malignant B-cells producing polyclonal high-affinity immunoglobulin G (IgG) antibodies that are directed against antigens on red blood cells and platelets, that lead to hemolytic anemia and immune thrombocytopenia, respectively(5).
And while single-agent fludarabine therapy can cause (hemolytic anemia (HA) and it is contraindicated in patients with hemolytic anemia ,Our patient had been treated successfully with combination of Rituximab and Cyclophosphamide combined Fudrabine therapy(FCR) and such a combination as FCR is suspected may not cause a similar degree of hemolysis. However, In the CLL8 trial(6) that randomized previously untreated CLL patients to either FCR or FC (fludarabine and cyclophosphamide), there was no difference in the incidence of hemolytic anemia in the two arms (<1%).
Interesting thing in our patient ,he developed Evans syndrome complicated FCR therapy four months after he completed his treatment ,despite what is known about fludarabine induce autoimmune hemolytic anemia during first few cycles and this is what had been registered in a large series of 24 patients who experienced severe and life-threatening HA during treatment with Fludrabine after either the first, second, or third cycle and in one patient during the six cycle had been be reported by Raymond B. Weiss et al.(7)
Our patient had severe anemia which showed no response to steroid treatment for three weeks and he retreated with Rituximab therapy. After the fourth course of Rituximab therapy patient did not need additional erythrocyte support with tapering steroid therapy. The management of Fludrabine induced hemolysis is not standard. and many choices including steroids have been used.There are some reports about the successful treatment of autoimmune phenomenon including pure red cell aplasia and AIHA by using Rituximab (8,9,10) and case report by Semra Paydas of patient with Fludarabine-induced hemolytic anemia who successfully treated by rituximab(11)
To the best of our knowledge we did not find a similarly treated case of Fludara combining therapy(FCR) complicated by autoimmune Evans Syndrome and re treated successfully by Rituximab .

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