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SHORT COMMUNCATION

Prompt and sustained response of a steroid-refractory autoimmune hemolytic anemia to a rituximab-based therapy in a chronic lymphocytic leukemia patient

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Abstract
Introduction Autoimmune hemolytic anemia (AIHA) is a rare and potentially life-threatening event which may complicate the course of chronic lymphocytic leukemia (CLL) at any time and steroid-refractory AIHA of CLL poses a therapeutic challenge for physicians. Here, we report the safety and efficacy of a rituximab-containing regimen in a CLL patient with steroid- and IVIg-refractory AIHA.
Case report A 57-year- old man affected by CLL, presented with fatigue, dyspnoea, tachycardia and jaundice. His physical examination revealed overt jaundice, hepato- and splenomegaly, and enlargement of lymph nodes in all superficial sites. The blood chemistry showed severe anemia (Hb value 3.9 g/dL), high white blood cell count (89×10^9/L), altered hemolysis markers and direct antiglobulin test (DAT) was positive for both complement and IgG. The patient failed to respond to both a 4-day course of high-dose dexamethasone IV (40 mg/day) and intravenous immunoglobulin (IVIg) (1 g/kg/day × 2 days). Thus, a schedule containing rituximab (375 mg/m^2 day +1), cyclophosphamide (750 mg/m^2 day +2) and prednisone (60 mg/m^2 from day +1 to day +7) (R-CP) were administered. Four cycles, repeated every 4 weeks, were administered. After 4 days from the infusion of this schedule, the patient showed a marked reduction of the lymphocytosis, and the hemoglobin level started to increase. No rituximab-related side effects were recorded. At the end of treatment DAT became negative and patient achieved a nodular Partial Remission (nPR).
Conclusion Our data showed the safety and efficacy of a rituximab-containing regimen in a life-threatening CLL-related AIHA, refractory to steroid and IVIg therapy. This schedule has allowed the patient to obtain a prompt and dramatic rise in hemoglobin level and a response to both AIHA and CLL.

Keywords CLL · AIHA · Therapy · Rituximab

Introduction

Autoimmune complications are common in CLL, occurring in up to a quarter of all patients during the course of the illness. By far, the most common manifestation is AIHA [1]. There is agreement that the treatment of AIHA in CLL is primarily based on immunosuppression with drugs, such as, glucocorticoids. Besides splenectomy that in any case has shown a limited efficacy in secondary AIHA [2], there are limited effective therapeutic options for CLL patients with steroid-refractory AIHA, although IVIg and immunosuppressive drugs have been used with varying degrees of success [3, 4]. Since the occurrence of AIHA is often associated with active CLL [1], probably as a consequence of the aberrant antigen presenting cells (APC) function by B-CLL cells [5], underlying CLL should be treated to resolve AIHA. The combination of chlorambucil with steroids represents a good therapeutic option for AIHA CLL-related patients; in fact 70% of patients treated with this approach achieved DAT negativity [1]. Recent encouraging data about the efficacy of rituximab, administered alone or in combination, for patient with CLL-related AIHA refractory to conventional treatment are reported, as reviewed by

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D'Arena [6]. These data are quite expected, since this monoclonal antibody, on one hand, has a cytotoxic activity against B-CLL lymphocytes, and on the other hand, binds to the Fc receptors on macrophages and thereby prevents the immune-mediated destruction of the autoantibody coated erythrocyte [7]. Here, we report the safety and efficacy of a rituximab-containing regimen in a case of CLL patient with steroid-refractory AIHA.

Case report

In February 2006, a 57-year-old American male was admitted to the Haematology Unit of Cosenza because of fatigue, dyspnoea, tachycardia and jaundice. He was referred with a diagnosis of Rai stage 0 CLL in 1998. In March 2004, he was treated with rituximab (375 mg/m^2 every week for a total of 4 courses) because of disease progression and achieving a partial response (PR). The patient showed stable disease up to January 2006. At the time of our first observation, physical examination revealed overt jaundice, hepato- and splenomegaly (10 cm below costal margin) and enlargement of cervical, axillary and inguinal lymphnodes (diameter ranking between 2 and 3 cm). The blood chemistry showed, life-threatening anemia (hematocrit 13.3%, Hb value 3.9 g/dL with high reticulocyte count (270×10^9/L), normal platelet count (185×10^9/L) and high white blood cell count (89×10^9/L with 80% lymphocytes and 12% neutrophils). Hemolysis markers indicated; bilirubin 4.8 mg/dL, lactate dehydrogenase 920 IU/L (normal value, below 450 IU/L), haptoglobin 5 mg/L and a DAT positive for both complement (4+/4+) and IgG (4+/4+). Peripheral blood lymphoid cells showed a typical morphology with a typical CLL phenotype (CD5+/CD19+/CD23+/CD79b-/FMC-7-/sIg weakly+). Bone marrow histology showed a diffuse pattern of CLL infiltration. Finally, CD19 neoplastic cells showed a negative expression of CD38 (3% of positive CLL cells) and somatic mutations of immunoglobulin heavy-chain variable genes were >2%.

Therapeutic strategy

The patient failed to respond to both a 4-day course of high-dose dexamethasone IV (40 mg/day) as well as a two-day course of IVIg (1 g/kg/day). During treatment, five selected and irradiated units of red blood cell transfusions were infused. No clinical or laboratory sign of transfusion reaction was documented. However, no significant improvement of the Hb level (4.0 g/dL) was noted. Therefore, a schedule containing rituximab (375 mg/m^2 day +1), cyclophosfamide (750 mg/m^2 day +2) and prednisone (60 mg/m^2 from day +1 to day +7) (R-CP) were administered. Allopurinol was also administered at a dose of 300 mg prior to starting the R-CP regimen and for 10 days thereafter. The patient was pre-medicated with paracetamol (1 g p.o.) and chlorpheniramine maleate (10 mg I.V.) before rituximab infusion. Infection prophylaxis was managed with daily administration of fluconazole 50 mg orally, acyclovir 200 mg orally every 8 h and trimethoprim–sulphamethoxazole orally two times a week. Four cycles, repeated every 4 weeks, were administered.

After 4 days from the first infusion of R-CP, the patient obtained a significant reduction of the lymphocytosis and the Hb level started to increase. No rituximab-related side effects were recorded. The follow-up is shown in Fig. 1. It is notable that Hb level dramatically improved after the first cycle and reached normal value at the end of four cycles of chemotherapy. Moreover, the patient showed a normalization of hemolysis markers (Hb, lactate dehydrogenase, haptoglobin and bilurubin levels and reticulocyte count were within range), and DAT became negative. Since he presented a physical examination and a TC scan negative as well as a nodular pattern of bone marrow histology, he was considered to be in nodular Partial Remission (nPR). After 18 months of follow-up, the patient is still in nPR and DAT remains negative.

Discussion

AIHA is a rare and potentially life-threatening event that may complicate the course of CLL at any time and

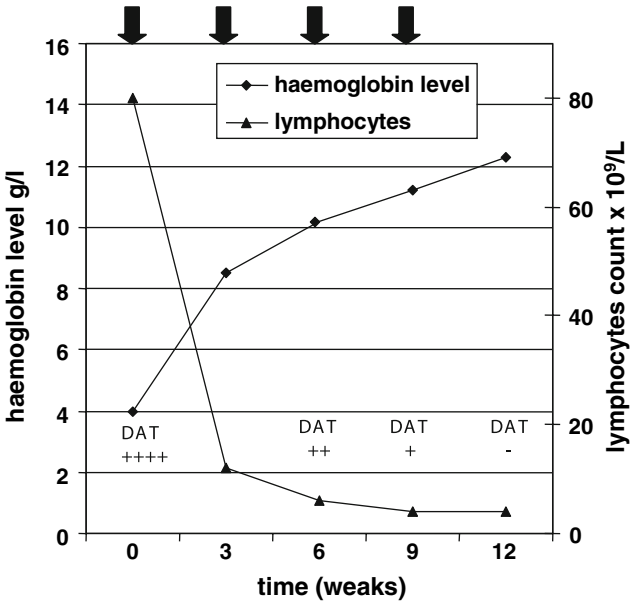

Fig. 1 Hemoglobin level, lymphocyte count, and DAT score during R-CP; *the arrows indicate* R-CP therapy and DAT, direct antiglobulin test

steroid-refractory cases pose a therapeutic challenge for physicians. In fact, there are no established and effective therapeutic options for these poor prognosis patients. Rituximab, an anti-CD20 monoclonal antibody, which has been proven to be an effective treatment both for CLL and autoimmune phenomena like autoimmune thrombocytopenic purpura (ITP) or AIHA, has shown its efficacy when administered alone or in combination in the management of CLL-related AIHA [6]. We reported a severe case of AIHA that complicates the course of CLL. The patient who presented with both life-threatening anemia (Hb 3.9 g/dL) and an active CLL did not achieve hemolysis stabilization with steroid and IVIg therapy. He underwent a rituximab-based regimen similar to that proposed by Gupta [8]. We have chosen this approach since it seems to guarantee a faster Hb normalization (roughly 2 months) [8], than chlorambucil (median, 4.5 months) [1] and rituximab alone (median, 4 months) [9]. Our data confirm the efficacy of a rituximab-based regimen in a severe case of CLL-associated AIHA [8]. After few days from the first infusion of R-CP, the patient obtained a prompt rise in the Hb level. This schedule was well tolerated and no episodes of grade 3–4 toxicity were observed. Moreover, at the end of the four cycles of therapy, the patient became DAT negative and achieved nPR. The patient is still in remission, both for AIHA and CLL, +18 months after being treated with R-CP regimen. These results are in line with those reported by Gupta [8]. In this series, all eight CLL patients responded to the treatment, with five also converting to DAT negativity and an optimal disease response was obtained (seven cases were in CR). Moreover, these data confirm the close relationship between the CLL-lymphocytes and AIHA, and as an effective treatment against CLL allows to resolve this autoimmune phenomena. In the resolution of this case, it is difficult to establish the contribution of each agent (rituximab, cyclophosphamide and prednisone). We can hypothesize that all the three drugs have determined both an effective immunosuppression and cytoreduction. These encouraging data confirm that this approach should be considered for CLL patients with steroid-refractory AHIA.

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