Complete remission of hairy cell leukemia variant (HCL-v) complicated by red cell aplasia post treatment with rituximab

Hairy cell leukemia variant (HCL-v) is a rare form of a chronic B cell lymphoproliferative disorder. Unlike typical hairy cell leukemia (HCL) where the complete response (CR) rate to 2-chlorodeoxyadenosine and 2'-deoxycoformycin can approach to about 90%, in HCL-v CR is rare and partial response (PR) occurs in approximately 50% with these agents. Rituximab treatment in relapsed or refractory HCL results in a CR of 13% to 53%, but its use in HCL-v has not been reported in the literature to our knowledge. We describe a patient with HCL-v, whose course was previously complicated by pure red cell aplasia who achieved CR after treatment with rituximab, and briefly review outcomes of treatments used in HCL-v in the current literature.

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To the editor:

Hairy cell leukemia variant (HCL-v) is a rare form of chronic B cell lymphoproliferative disorder which responds poorly to conventional treatment used in typical hairy cell leukemia (HCL).[1,2] Partial Response (PR) occurs in about 50% to treatments such as 2-chlorodeoxyadenosine (2CdA) and 2'-deoxycoformycin [2]and complete response (CR) is rarely described in the literature. Although rituximab have been reported to induce CR in 13% and 53% in two series,[3,4] its use in HCL-v has not been reported in the literature to our knowledge. We describe a patient with HCL-v, who achieved CR after treatment with rituximab and briefly review outcomes of treatments used in HCL-v in the current literature. In April 1997, a 75 year-old caucasian man with bladder carcinoma treated with local radiotherapy was referred for investigation of lymphocytosis. Examination revealed splenomegaly 11cm below costal margin (BCM) and minimal generalised lymphadenopathy. Hb was 12.8g/L; WCC 28.9×10^9/L; lymphocytes 17.3×10^9/L; platelets 136×10^9/L. Blood film revealed abundant lymphoid cells with round nucleus, prominent nucleoli and basophilic villous cytoplasm. Bone marrow aspirate and trephine (BMAT) showed a dense interstitial lymphoid infiltrate with medium cells containing moderate cytoplasm. Immunohistochemistry revealed CD20 and DBA44 positivity. Moderate reticulin fibrosis was present. Flow cytometry confirmed a monoclonal B-cell population with the phenotype: $CD5^-$,10^-,19^+,20^+,22^+, $11c^+$,103^+, $FMC7^-$,$CD25^-$ with κ light chain restriction, which in conjunction with morphology was diagnostic of HCL- v. The patient was observed for 8 months before he re-presented with Hb 64g/L, WCC 35.7×10^9/L; platelets 223×10^9/L. Red cell aplasia was diagnosed on the basis of <1% erythroblasts on repeat BMAT and a reticulocyte count of 0.2%. Upon unsuccessful trials of treatment with prednisolone (50 mg/d), 2CdA(0.1 mg/kg/d for 7 days), IFNα(3 mU three times per week), and cyclophosphamide (100 mg/o/d for 3 months) respectively, splenectomy was undertaken resulting in 4 months of transfusion independence. Splenic histology showed diffuse red pulp infiltration of intermediate sized lymphoid cells in keeping with histology described in HCL-v.[9] The patient's subsequent clinical course is shown in Figure 1. In August 2001, rapid progression occurred with WCC of 100×10^9/L; platelets 40×10^9/L; Hb 77g/L. Rituximab was commenced (375 mg/m^2 IV weekly for 4 weeks) with prompt response. After 4 treatments of rituximab, Hb improved to 104×10^9/L, platelets increased to 184×10^9/L, and WCC 7.6×10^9/L, with no abnormal lymphoid forms seen on blood film. BMAT performed 4 weeks post rituximab treatment was normocellular with normal trilineage haematopoiesis and no residual lymphoid infiltration consistent with complete morphological response to therapy. Transfusion independence was achieved from this first treatment with rituximab. Thirteen months later, relapse occurred with lymphocytosis of 48×10^9/L; BMAT revealed lymphoid infiltrate comprising 69% of nucleated cells, with widespread CD20 and moderate DBA-44 positivity on immunohistochemistry. Rituximab 375mg/m^2 IV weekly for 3 doses was again given. Lymphocyte count promptly decreased to 2.8×10^9/L with repeat BMAT again showing CR. This response lasted 10 months prior to relapse with reappearance of variant hairy cells on blood film, lymphocytosis of 27×10^9/L and neutrophil count of 0.14×10^9/L. Re-treatment this time with rituximab resulted in only a minor response. He died from progression of HCL-v with extensive abdominal infiltration and ascites. HCL-v is a rare and distinct clinicopathological entity which tends to be resistant to conventional treatments used in typical HCL. Table 1 shows that CR has only been described in only one of 17 patients treated with 2CdA and has not been described at all with IFNα, 2'deoxycoformycin, fludarabine,CHOP nor splenectomy. Consistent with past reports, our patient demonstrated no response to initial treatment with 2CdA and IFNα. Only a transient PR to splenectomy was achieved. Unexpectedly, a 13 months CR was achieved with rituximab and a second CR was sustained for 10 months. Interestingly, rituximab resistance was demonstrated upon third re-treatment despite the leukemia remaining $CD20^+$. Rituximab is a chimeric immunoglobulin monoclonal antibody that targets CD20 antigen expressed on most B cell leukemias and lymphomas.[7] It's efficacy in refractory or relapsed HCL have been well documented, possibly due to the higher CD20 antigen density exhibited by HCL compared to other lymphoid malignancies.[8] HCL-v also exhibits CD20, but the use of rituximab to our knowledge has never been reported before. The one recent report of CR using rituximab was actually in HCL-Japanese variant, another distinct variant of HCL, which, like HCL-v, is characteristically CD $11c^+$, always $CD25^-$, and occasionally $CD103^-$.[10] However, it is uniquely described in the Japanese popula-

Figure 1. WCC, lymphocyte count, and Hb trend post treatment with rituximab.

tion, mainly in females, and characterised morphologically by mononuclear cells with long microvilli and prominent membranous ruffles as seen under electron microscopy. This patient with HCL-Japanese variant proved refractory to pentostatin and cladribine, and like our patient, responded promptly to rituximab with CR for 18 months.[11]

Up to date, 2CdA has been the only drug known to induce CR in HCL-v.[2] We now report the first case of HCL-v with CR to treatment with rituximab. Given the high relapse rate both in previous experience and in this reported case, and given the acquired resistance to repeated treatments of rituximab seen in our case, we propose that rituximab used in conjunction with 2CdA could be explored further in future studies to achieve a longer lasting remission.

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