Clinical and molecular complete remission in a case of variant hairy cell leukemia treated with DHAP followed by high-dose chemotherapy plus rituximab

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Variant HCL (v-HCL) is a disorder with a worse prognosis than typical HCL, whose outcome has been greatly improved by the introduction of α-IFN and purine analogues. A few cases of v-HCL treated with 2'-deoxycoformycin, cladribine and/or splenectomy have been published,[1,3] but the response rates are lower than in typical HCL and often poor, although some authors have described a median survival of nine years.[4] We here describe a case of aggressive relapsed v-HCL efficaciously treated with DHAP followed by high-dose chemotherapy (HDT) plus autologous stem cell transplantation supported by peripheral blood stem cells (PBSCs) collected after *in vivo* purging with rituximab. In April 1999, a 53-year-old man was referred to our institution because of symptomatic splenomegaly in the absence of superficial lymph adenopathies. He presented thrombocytopenia (96×10^9 cells/L) and mild lymphocytosis (3.9×10^9 cells/L). Peripheral blood and bone marrow cytomorphology and histology were highly suggestive of v-HCL (Figures 1a and 1b), which was subsequently confirmed by immunophenotype analysis (CD20+, CD103+, CD11c bright, CD25 negative, bright IgM/Dλ sIg). Cytogenetic analysis showed a complex karyotype involving chromosomes 2 and 8 - t(2;8)(q23;q22) - and chromosomes 7, 14 and 17. He was initially treated with 2'-deoxycoformycin (4 mg/m^2, six cycles every two weeks and the two monthly cycles). Despite a good partial marrow response (persistence of 5-10% variant hairy cells), the splenomegaly remained substantially unchanged. After a short and inefficacious course of α-IFN (3 MU thrice weekly for two months), the patient underwent splenectomy (weight: 3800 g). The histology was consistent with v-HCL, and the immunophenotype of the neoplastic spleen cells was similar to that reported at diagnosis (Figure 1c); a core hepatic biopsy showed HC infiltrates, predominantly in the sinusoids. After remaining indolent for one year, the disease aggressively relapsed with deep and superficial lymph adenopathies (bulky in the axillae), leukocytosis (WBC 70.0×10^9/L) sustained by variant hairy cells, and diffuse bone marrow involvement. Axillary lymph node biopsy confirmed v-HCL involvement with the known phenotype (Figure 1d). The patient was first treated with two APO cycles (doxorubicin, prednisone, oncovin) cycles to explore the possibility of HDT but, as the response was minimal, he was put on a outpatient DHAP-like regimen (cisplatin 70 mg/m^2 over three hours on day 1, Ara-C 1.5 g/m^2 over three hours on days 2-3, dexamethasone 40 mg i.v. for four days). Given the very good therapeutic results obtained after four cycles (WBC 8.7×10^9/L, with 5% of CD20/CD103/λ B cells; >80% reduction in lymph adenopathies), the fifth cycle was administered with G-CSF (5 μg/kg during the first five days and 10 μg/kg until apheresis) and rituximab infusions (375 mg/m^2 on days 3 and 10) with the aim of collecting purified PBSCs. Successful leukapheresis was performed on day 16 (CD34 cells: 7.9×10^6/kg). The presence of residual hairy cells in the PBSCs was excluded (detection limit: 10-5) by assessing DNA samples of the leukapheresis products using semi-nested PCR amplification of the clonal rearrangement of IgH genes (20mer anti-sense allele-specific oligonucleotide (ASO) primers from the CDRIII regions, including the N-insert). One month later, the patient received melphalan 200 mg/m^2 and thiotepa 15 mg/kg, followed by an autologous stem cell infusion. His peripheral blood counts recovered on day +17. Two more rituximab infusions (375 mg/m^2) were administered on days +30 and +37. A molecular and clinical complete remission was documented three months after HDT and persists after 16 months. This case offers a number of interesting points. A conventional regimen (DHAP) that has been previously used as a pre-HDT salvage treatment in relapsed aggressive NHL[5] and, more recently, in a successful schedule for the treatment of mantle cell lymphoma,[6] proved to be extremely efficacious in this case of advanced v-HCL whereas a CHOP-like regimen (APO) failed. The sequential use of anti-CD20 monoclonal antibody allowed us to collect molecularly purified PBSCs, thus extending the therapeutic role of rituximab to v-HCL after its previous successful use in typical HCL.[7-9] This case of refractory/relapsed v-HCL also shows the efficacy of myeloablative chemotherapy supported by tumour-free stem cell products, as has been described in low-grade NHL.[10] The good results of this sequential therapy are particularly interesting because 2'-deoxycoformycin, α-IFN and splenectomy failed to attain a lasting response. Despite the short follow-up, we think that this therapeutic approach is useful and worth evaluating in other similar cases.

Figure 1. a) Peripheral blood smear: Neoplastic cells with round or oval nuclei, prominent central nucleoli and moderate amounts of cytoplasm with villous projections (magnification x100). b) Bone marrow biopsy: Peritrabecular localisation of medium-sized neoplastic cells, with ample clear cytoplasm and central nucleoli c) Spleen: Diffuse red pulp infitration by neoplastic CD20+ cells (Immunoperoxidase; magnification x40) d) Lymph node: Variant hairy cells expressing the DBA.44 B-cell antigen (Immunoperoxidase; magnification x40).

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