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High Curative Potential of Ibrutinib in Hairy Cell Leukemia Variant Refractory to Conventional Chemotherapy: A Case Report

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Abstract

Hairy cell leukemia (HCL) is a chronic lymphoproliferative disorder with a high sensitivity to purine nucleoside analogues (PNAs). Its uncommon variant form (HCLv) has a more aggressive clinical course and an intrinsic resistance to chemotherapy. Target therapies like Bruton tyrosine kinase inhibitors (BTKi) are under investigation. We present a case of a 62-years-old female with HCLv presenting with splenomegaly and hyperleukocytosis. She was resistant to multiple standard chemotherapy regimens but responded well to the BTKi ibrutinib, obtaining the normalization of blood counts and splenomegaly without significant toxicities and despite intercurrent SARS-CoV-2 infection.

Case report

Hairy cell leukemia (HCL) is an uncommon hematologic disorder characterized by pancytopenia, splenomegaly and the presence of clonal lymphocytes with irregular ("hairy") cytoplasm, usually harboring BRAF V600E mutation. Its variant form (Hairy cell leukemia variant, HCLv) is less frequent, has a more aggressive clinical presentation often with leucocytosis and massive splenomegaly, and lacks BRAF V600E mutation andthe typical immunophenotypic hallmarks of HCL (CD25, CD123 and CD200). Recentlypublished 5th edition of WHO Classification of Haematolymphoid Tumours incorporates HCLv into "Splenic B-cell lymphoma/leukaemia with prominent nucleoli" cathegory, because of the typical HC nuclear morphology [1].

Purine nucleoside analogues (PNA) like cladribine and pentostatine are very effective with complete responses that last for years in about 90% of the patients [2]. PNAs ± the anti-CD20 rituximab can be used in case of relapse after a long lasting response [3]. BRAFinhibitor vemurafenib ± rituximab are an effective choice in case of BRAF V600E mutation. Chemoimmunotherapy like rituximab + bendamustine or target therapies like anti- CD22 immunotoxin moxetumomab pasudotox or BTK inhibitors (BTKi)demonstrated efficacy in relapse/refractory disease.

Standard treatments are not as effective in HCLv, which has got intrinsic resistance to chemotherapy [4].

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Here we present a case of a female patient with relapse/refractory HCLv treated successfully with the BTKi ibrutinib.

P. P., 62 yo, no significant past medical history, came to our institution in July 2018 for mild splenomegaly (13 cm) and lymphocytosis (WBC 30.000/mm3, Lym 19.230/mm3).A peripheral blood smear revealed numerous lymphoid elements with short and squat cytoplasmic protrusions, some with a distinct nucleolus. Peripheral blood immunophenotyping suggested a variant form of HCL (CD103/CD19/CD20/CD22/CD11c/CD49d/CD79b/FMC-7 positive, CD23/CD25/CD5/CD200 negative, kappa light chain restricted), confirmed with a bone marrow biopsy. BRAF V600E mutation was not detected neither in the peripheral bloodnor in the bone marrow.

Lacking criteria for treatment, we chose a watch & wait strategy.

In October 2020 she came with worsening symptomatic splenomegaly (19 cm) and a 4- fold increase in lymphocyte count compared with disease onset (Hb 12.4, GB 146.000/mm^3, Lym 99.000/mm^3, LUC 36.000/mm^3, PLT 293.000/mm^3).

We chose the standard of care cladribine at a dose of 0.12 mg/kg/die intravenously for five consecutive days. A disease re-evaluation performed 6 months after treatment (April2021), in line with HCL European guidelines [5], revealed reduced but persistent lymphocytosis (GB 17.550/mm^3, Lym 9.880/mm^3, LUC 3.150/mm^3, PLT 223.000/mm^3) and worsening splenomegaly (21 cm). Considering the poor response to PNAs, we starteda second line chemotherapy with rituximab-bendamustine for 6 cycles. Rituximab infusions were discontinued in all the 6 cycles because of infusion related reactions. Despite an initial control of leucocytosis, at the end of treatment (December 2021) splenomegaly was not improved and lymphocyte count again increased.

We started a third-line chemotherapy with CHOP-21 (cyclophosphamide, doxorubicine, vincristine, prednisone every 21 days) with the aim of debulking the disease and as a bridge to a subsequent target therapy and/or splenectomy depending on response. However, due to the lack of an objective response, CHOP-21 was discontinued after the third cycle.

Considering the complete resistance to 3 lines of chemotherapy, we started a target therapy with the BTKi ibrutinib, obtained as compassionate use, at the standard dose of 420 mg/die as reported in a phase 2 study by Rogers et al.

Prior to the start of treatment, there were severe splenomegaly (22 cm), anemia and lymphocytosis (Hb 9.1, WBC 21.310/mm^3, Neu 7.420/mm^3, Lym 8.030/mm^3, PLT125.000/mm^3). We performed a bone marrow aspirate to evaluate the presence of MYD88 L265P mutation, predictive of response to ibrutinib in other chronic lymphoproliferative disorders like lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia [6]), which was not detected. Molecular testing for TP53 and IGHVmutational status on peripheral blood revealed wild type p53 and unmutated IGHV profile.

She didn't develop redistribution lymphocytosis, which remained stable, whilst anemia improved in the first 30 days of treatment (Hb 11.0 g/dl).

No cutaneous, gastro-intestinal or cardiovascular toxicities were observed with ibrutinib.At the end of the second month, there was a normalization of the WBC count (Hb 11.1 g/dl, WBC 7.420/mm^3, Neu 3.520/mm^3, Lym 3.410/mm^3, PLT 269.000/mm^3).

Since an anti- SARS-CoV-2 Spike protein antibody test showed no significant IgG humoral response, according to the European Medicine Agency guidelines, the anti- SARS-CoV-2 monoclonal antibodies tixagevimab and cilgavimab were administered as pre-exposure prophylaxis, without discontinuing ibrutinib. Nevertheless, ten days later she developed fever and cough and tested positive for SARS-CoV-2 (antigenic test). A chest-CT showed pneumonia that required hospitalization. She immediately startedspecific coronavirus treatment with nilmatrevir/ritonavir for 5 days. Despite the possiblestrong pharmacokinetic interaction with ritonavir, ibrutinib wasn't stopped, because of the first evidence of haematological disease control in our patient and the possible therapeutic role of BTKi for Coronavirus-19 disease [7]. Respiratory symptoms rapidly improved without oxygen supplementation and she was discharged. The antigenic test resulted negative after 25 days of infection.

After three months (20 May 2022), CBC showed stable normal leukocyte count and an abdomen ultrasound showed a significant reduction of splenomegaly (14 cm) (**Figure 1**). In June 2022, after four months of treatment, bone marrow biopsy shows minimal residual infiltration by HCLv (5-10% of cellularity) with persistent normal CBC and no palpablesplenomegaly.

This case underlines the growing importance of target therapies in chronic lymphoproliferative disorders. HCLv has a distinct clinical and biological profile compared to its classic counterpart and could be considered an independent disease.

BTKi inhibits Bruton's tyrosine kinase (BTK) by binding covalently to a cysteine residuein the kinase domain. BTK is uniformly expressed in normal B-lymphocytes and in HCLcells, too. Its inhibition blocks pathways that are essential for hairy cells' proliferation and survival and for the interactions with the bone marrow microenvironment (like CXCR4 and MAPK/ERK pathways) [8].

Ibrutinib is the first in class oral BTKi, well known for the treatment of B-cell lymphoproliferative disorders like mantle cell lymphoma, marginal zone lymphoma andespecially chronic lymphocytic leukaemia.

Few data are available for ibrutinib in HCL and mostly derive from case reports [9]. Ibrutinib was tested in a phase 2 trial in 37 patients mostly with relapsed/refractory (R/R)HCL or HCLvAll of them had previously received PNAs and were heavily pretreated (median number of prior treatments 4, range 0–12). The ORR at 32 weeks was 24%, increasing to 36% at 48weeks and to 54% at any time starting ibrutinib. Complete response (CR), partial response (PR) and stable disease (SD) were 24%, 43% and 33% ofthe patients at any time during study, respectively. The overall response rate (ORR) was27% in HCLv. Despite this trial was not powered to identify a significant difference in efficacy in classic and variant HCL, response rates and survival outcomes were not statistically different between the two forms. Toxicities were mostly cardiovascular and gastrointestinal, with frequencies in line with experiences in other lymphoproliferative disorders.

In our patient, molecular testing performed before the start of target therapy showed an unmutated IgHV mutation status and, surprisingly, the absence of TP53 alterations. In fact, HCLv frequently shows mutant p53, that confers resistance to chemotherapy.

Our patient showed a clear sensitivity to target therapy, due to the strong dependence of neoplastic lymphoid cells on the

survival pathways linked to BTK. Moreover, shedramatically responded to ibrutinib despite the absence of MYD88 L265P mutation.

Despite a low rate of deep responses, ibrutinib could be an effective and safe option in asetting with few therapeutic choices like R/R HCLv. Our case is a typical prototype of this concept: She failed 3 lines of chemotherapy in 10 months but showed an early dramatic response to ibrutinib. However, more data are required from clinical trials to establish ibrutinib as a potential standard of care in R/R HCL-HCLv and to find biological features that could predict its efficacy.

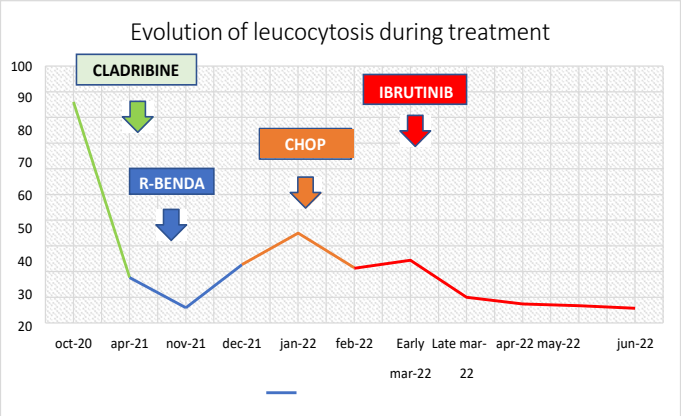

Figure 1: Evolution of leucocytosis during different lines of chemotherapy and with ibrutinib..

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