Abstract

Disease Overview: Hairy cell leukemia (HCL) and HCL-like disorders, including HCL variant (HCL-V) and splenic diffuse red pulp lymphoma (SDRPL), are a very heterogeneous group of mature lymphoid B-cell disorders characterized by the identification of hairy cells, a specific genetic profile, a different clinical course, and the need for appropriate treatment.

Diagnosis: Diagnosis of HCL is based on morphological evidence of hairy cells, an HCL immunologic score of 3 or 4 based on the CD11C, CD103, CD123, and CD25 expression, the trephine biopsy which makes it possible to specify the degree of tumoral medullary infiltration and the presence of BRAFV600E somatic mutation.

Risk Stratification: Progression of patients with HCL is based on a large splenomegaly, leukocytosis, a high number of hairy cells in the peripheral blood, and the immunoglobulin heavy chain variable region gene mutational status. VH4-34-positive HCL cases are associated with a poor prognosis.

Treatment: Patients should be treated only if HCL is symptomatic. Chemotherapy with risk adapted therapy purine analogs (PNAs) are indicated in first-line HCL patients. The use of chemo-immunotherapy combining PNAs and rituximab (R) represents an increasingly used therapeutic approach. Management of relapsed/refractory disease is based on the use of BRAF inhibitors (BRAFi) plus rituximab or MEK inhibitors (MEKi), recombinant immunoconjugates targeting CD22 or Bruton Tyrosine Kinase inhibitors (BTKi). However, the optimal sequence of the different treatments remains to be determined. The Bcl2-inhibitors (Bcl-2i) can play a major role in the future.

1 INTRODUCTION

Hairy cell leukemia (HCL) is recognized as an entity by the World Health Organization since 2008 and in the last 2017 revision of the WHO classification of lymphoid neoplasms. HCL, four to five times more frequent in men than women, accounts for 2% of all leukemias with approximately 1.100 new HCL cases in the United States. The few available population-based studies are limited. When including HCL and HCL-like disorders, the overall age-adjusted to the 2000 US population incidence rate is 0.7 per 100 000 in men and 0.3/100 000 in women. When adjusting to the worldwide population, the incidence rate of HCL is 0.3 and 0.1/100 000, respectively, and remains relatively stable over time. It is lower in non-Hispanic/black, Hispanic, or Asian/pacific Islander. Despite an improvement of overall (OS) and relative survival (RS), a significantly lower OS is observed among African American individuals compared with other ethnic groups. The mortality rates for patients with HCL is similar to those of the general population 5 years after diagnosis. HCL must be differentiated from other
HCL-like disorders, including hairy cell leukemia variant (HCL-V)\textsuperscript{10,11} and splenic diffuse red pulp lymphoma (SDRPL).\textsuperscript{12} In this article, we will review the significant strides over the last 3 years in the understanding of the pathobiology of HCL and HCL-like disorders and update the new treatment procedures now available particularly for patients with relapsed/refractory HCL.

2 | HOW THE DIAGNOSIS OF HAIRY CELL LEUKEMIA AND HCL-LIKE DISORDERS IMPROVED IN DAILY PRACTICE?

The median age of patients with HCL is 63 years old in men and 59 in women. HCL can rarely occur in adolescence.\textsuperscript{13} At diagnosis, HCL is usually characterized by infections, splenomegaly, or the presence of cytopenias. Autoimmune or unusual clinical manifestations are occasionally reported as bulky abdominal lymph nodes, pleural effusions and ascites, skin lesions\textsuperscript{14} or destructive bone lesions some of which can mimic multiple myeloma.\textsuperscript{15,16} With the high frequency of routine peripheral blood analyses, hairy cells can also be detected in asymptomatic patients. Complete blood count and careful review of the peripheral blood smear are the first step in the very characteristic morphological identification of hairy cells (Figure 1A). The HCL immunophenotypic profile is characterized by the clonal expansion of mature B-cells arrested at a late stage of differentiation showing a strong light chain restricted surface immunoglobulin with a typical immunophenotype: bright expression of CD19, CD20, CD22 and CD200. Hairy cells are usually negative for CD5, CD23, CD10 and CD27 and positive for CD11c, CD103, CD123, and CD25. An immunological score was proposed with one point given to each of the last four markers when it is expressed and no point when it is not expressed. A score of 3 or 4 is observed in 98% of cases of HCL, whereas in other HCL-like disorders the score is usually low: 0 or 1.\textsuperscript{17} The aberrant expression of CD5,\textsuperscript{18} CD10\textsuperscript{19} or loss of expression of CD123\textsuperscript{20} has been rarely reported. In the international consensus guidelines, the interest of trephine bone marrow biopsy and/or aspiration has been emphasized to appreciate the degree of tumor infiltration and help diagnosis in complex cases (immunostaining with CD20, CD72 and annexin-A1).\textsuperscript{21}

HCL has to be distinguished from splenic B-cell lymphoma/leukemia, unclassifiable\textsuperscript{22} including HCL-V, SDRPL, and also splenic marginal zone lymphoma (SMZL). HCL-V is a provisional entity\textsuperscript{22} representing 800 new incident cases in the United States.\textsuperscript{2} The circulating abnormal lymphoid cells have a morphology intermediate between prolymphocytes and hairy cells (Figure 1B). The HCL immunological score is low (0 or 1): There is no expression of CD25 and CD200. CD123 expression is inconstant and weak.\textsuperscript{10,11} SDRPL is also a provisional entity and is very close if not identical to HCL-V. A large proportion (median: 60%) of small to medium-sized villous lymphoid cells is present in the peripheral blood. The abnormal lymphoid cells have a polar distribution of the villi and the nucleolus is small or not visible. The monoclonal B-cells express CD11c (97%), inconsistently CD103 (38%) and rarely CD123 (163%) or CD25 (3%).\textsuperscript{12} The CD200/CD180 median fluorescence (MFI) ratio may be helpful to distinguishing HCL from SDRPL, with a ratio of 0.5 or less in favor of SDRPL.\textsuperscript{23} In SMZL, the typical cell morphology describes abnormal lymphoid cells with round nuclei, condensed chromatin, and basophilic cytoplasm with polar short villi (so-called “villous lymphocytes”) in the peripheral blood. Heterogeneity in blood morphology is common, ranging from small lymphoid cells without specific features, to various degrees of monocytoid and plasmacytoid differentiation. A scoring system based on CD11c, CD22, CD76, CD38 and CD27 expression was designed to differentiate SDRPL from SMZL.\textsuperscript{24} SMZL develops in the white pulp with a biphasic picture; lymphoma cells may involve the red pulp in patchy or diffuse fashion, with subsequent spread to the sinuses.

3 | WHAT HAS RECENTLY IMPROVED UNDERSTANDING OF HAIRY CELL LEUKEMIA AND HCL-LIKE DISORDERS?

3.1 | \textbf{BRAF} \textsuperscript{V600E} mutation: An early and central genetic driver in HCL

Using whole-exome sequencing (WES) in 2011, \textbf{BRAF}\textsuperscript{V600E} somatic mutation was found in a patient with HCL\textsuperscript{25} B-raf proto-oncogene (\textbf{BRAF} gene) (7q34) is composed of 18 exons: The mutation occurs in exon 15 at position 1799, in which thymine and adenine are exchanged, leading to valine (V) being substituted by glutamic acid (E) at codon 600 (V600E) of the \textbf{BRAF} protein. The mutation was subsequently identified in up to 80%-100% of HCL cases. The \textbf{BRAF}\textsuperscript{V600E} mutation constitutively activates \textbf{BRAF} by autophosphorylation of the protein and downstream MEK-ERK signaling pathway, leading to increased expressions of genes involved in survival and proliferation such as members of the ETS family, FOS, MYC as well of genes involved in MEK/ERK inhibition such as dual-specificity phosphatases (DUSPs).\textsuperscript{26} \textbf{BRAF}\textsuperscript{V600E} mutation is recurrent in various solid tumors,
including cutaneous melanoma, lung, ovarian, bladder, thyroid, prostatic cancers, cholangiocarcinoma and sarcoma/GIST. BRAF mutations have also been identified in other B-cell chronic lymphoproliferative disorders, chronic lymphocytic leukemia (PLL) and multiple myeloma in < 5% of cases. The mutation is now considered as the molecular hallmark of the disease representing a novel diagnostic possibility and option for therapeutic targeting of BRAF, using BRAF inhibitors (BRAFi). The absence of mutation of the BRAF gene (BRAFwt) is reported in up 10%–20% of patients with HCL: BRAFwt HCL patients could constitute a heterogeneous subgroup of HCL patients with poor prognosis and the possibility of mutations in exon 11 (F468C, D449E) should be excluded. Mutations in MAP2K1 encoding MEK (downstream protein of B-RAF) were found in more than half of the cases. MAP2K1 mutations also activate MAPK pathway. Note that some mutations allow the use of MEK inhibitors (MEKi), whereas others involving the binding site of the inhibitor, can lead to resistance.

3.2 Why a morphology with hairy cells?

The hairy cells overexpress various cytoskeleton components such as actins, intracellular phosphophositides as well members of the Rho family of small GTPases involved in active cytoskeleton organization. Unlike HCL-like disorders, in vitro exposure of primary HCL cells to BRAFi and MEKi can induce marked dephosphorylation of Rho family of small GTPases involved in active cytoskeleton organization. As actins, intracellular phosphoproteins as well as members of the

3.3 Cellular origin of HCL?

HCL is a fascinating disease and the normal counterpart of hairy cells is still unclear. HCL cells have a phagocytic activity when exposed to bacteria. Late-activated post-germinal center memory B-cells and possibly splenic marginal zone B-cells are considered as the cell of origin for HCL, even if splenomegaly is a result of red-pulp hypertrophy, whereas the white pulp becomes atrophic. DNA methylation profiling performed in 41 mature B-cell tumors including 11 HCL is also in favor of a post-germinal origin of hairy cells. Furthermore, a mutated profile of the immunoglobulin heavy chain variable (IGHV) regions is detected in 90% of HCL, SDRPL, and SMZL patients, indicating the cells must have transited through the germinal center. Conversely, the profile is mutated in one third of HCL-V. Molecular analysis of the repertory of the IGHV and the pattern of somatic hypermutations (SHM) show a different preferential use of VH3, VH3-30 (8%–23% of cases), or VH3-23 (3%–17% of cases) in HCL, VH4-34 in HCL-V, SDRPL and HCL with BRAF wild type (BRAFwt) and VH1-2 in SMZL. The BRAF gain-of-function mutation occurs also in earlier differentiation stages including hematopoietic stem cells (HSC) or B-cell lymphoid progenitors of affected HCL patients. When BRAF mutated HSC were transplanted into immunodeficient mice, none of those developed the full phenotypic picture of HCL suggesting the requirement of additional cooperating genetic alterations. In addition, expression of BRAF-V600E in murine hematopoietic stem/progenitor cells can cause hairy cell leukemia-like disease. BRAFV600E was also found in Langerhans cell histiocytosis (LCH) and Erdheim Chester disease (ECD) and a patient with LCH associated with HCL was recently described, suggesting the possibility of a relationship between HCL and LCH. How ever, the pattern of distribution of mutant alleles in the mononuclear compartment and bone marrow was clearly different between patients with HCL and LCH/ECD. In LCH/ECD, the majority of mutant alleles were present in CD14+ classical monocytes, CD16+ non-classical monocytes and CD11c+ myeloid dendritic cells in the peripheral blood. They are also distributed in HSCs and myeloid progenitors in the bone marrow. In HCL, the mutant alleles are not found in monocytes and myeloid cells but are detected in normal B and NK cells.

3.4 Other genes are recurrently mutated and play a role in the progression of the disease

More than 80% of benign nevi of the skin carry oncogenic BRAF mutations while never experiencing malignant transformation (Table 1). These data suggest that cooperating genetic and/or epigenetic events are required to facilitate malignant transformation. Sequencing of sequential BRAF samples at diagnosis and relapse demonstrated the emergence of new mutations at relapse. Alterations of cell cycle are essential in the pathology. In addition to the overexpression of cyclin D1, recurrent inactivation of the cell cycle inhibitor CDKN1B/p27 was identified in more than 10% of cases. Although TP53 mutations and/or del(17p) seem infrequent in HCL, it is recommended to assess TP53 status in case of PNA resistance. Inactivating KLF2 mutations were observed in 15% of HCL and 30% of MZL. KLF2 is a transcription factor controlling the differentiation of multiple B-cell subpopulations, including marginal zone B-cells. Mutations of the genes of the epigenetic regulation genes were frequently observed, with mutations in the histone methyltransferase KMT2C (MLL3) occurring in 15% of patients and more rarely mutations in histone demethylase KDM6A or histone acetyltransferase CREBBP (CBP). Others mutations in the chromatin remodeling complex family ARID1A, ARID1B were also described.
| Genomic data in HCL-like disorders |

**3.5.1 | High prevalence of MAP2K1 mutations in HCL-V and IGHV4-34-positive HCL**

The absence of mutation of BRAF in HCL-V, suggests that HCL and HCL-V could represent two different entities (Table 1). Activating mutations in MAP2K1 gene (15q22.1-q22.3) were found in VH4-34+ HCL (5/7 pts) and HCL-V (CD103+, CD25-) either IGHV4-34-negative (6/15 pts) or IGHV4-34-positive HCL-V (4/9 pts). In contrast, MAP2K1 mutations were identified in only 1/20 cases of IGHV4-34-negative HCL patients.\(^{31}\) In HCL-V, the identification of MAP2K1 mutations is an argument for the diagnosis but its presence is detected in only 50% of cases.

**3.5.2 | High prevalence of CCND3 and U2AF1 mutations in HCL-V**

In contrast to HCL, mutations of CCND3 were observed in 13% of HCL-V cases,\(^{47}\) a frequency identical to that observed in SMZL and less than 25% in SDRPL.\(^{53,55}\) CCND3 mutations involve the regulating PEST domain leading to cyclin D3 overexpression. Recurrent hotspot mutations of U2AF1 encoding a protein belonging to the spliceosome, were detected in 15% of HCL-V.\(^{31,47}\)

**3.5.3 | Recurrent genetic alterations in SDRPL**

Most cases display a mutated IGHV status, with a selective VH gene usage and overrepresentation of VH4-34.\(^{56,57}\) Few cases of NOTCH2 mutations (4/42 pts, 10%) were described, as well as in SMZL (8/47, 17%).\(^{53}\) In contrast, 24% of patients with SDRPL (6/25 pts) presented mutations in CCND3. The expression of CCND3 was present in more than 50% of the neoplastic cells in 24/37 splenectomy specimens, while it was rarely observed in CLL, SMZL, HCL, or blastic mantle cell lymphoma.\(^{55}\) Recently, recurrent mutations or losses in BCOR (gene encoding the BCL6 corepressor) were identified in 10/42 SDRPL (24%), whereas it was rarely observed in SMZL cases (2%). Compared to SMZL, KLF2 mutations were rarely observed (2%), and TNFAIP3 and MYD88 mutations were absent in SDRPL.\(^{53}\) The recent data highlight the genetic differences between all these entities with a possibility to develop novel therapeutic approaches.
3.6 Risk stratification in HCL

Splenomegaly > 3 cm above the normal, leukocytosis (> 10^9/L) and hairy cells in the blood (> 5 x 10^9/L), high beta2-microglobulin (> 2 N), and increased LDH are associated with a bad prognosis and resistance to purine analogs (PNA). Like CLL, CD38 expression drives poor prognosis. The IGHV mutational status has prognostic implications in HCL. The patients with unmutated IGHV have shorter overall survival durations than those with mutated. Furthermore, 40% of HCL-V and 10% of HCL patients use the IGHV4-34 immunoglobulin variable heavy chain rearrangement. VH4-34 positive HCL cases represent a subset and a new variant of HCL, associated with poor prognosis: higher disease burden at diagnosis, poor response to standard therapy, shorter overall survival (OS) and absence of BRAFV600E mutation.

4 UPDATE ON HCL TREATMENT AND HCL-LIKE DISORDERS

Varied treatment options are available (Figures 2 and 3) and recently changed. A meta-analysis was recently conducted to support efficacy of all the treatments mentioned in the review.

Watch-and-wait strategy sometimes with a duration of several years is required in about 10% of asymptomatic HCL patients. Patients should be treated, only if they are symptomatic and have symptoms from the disease or if the hematologic parameters are declining. The hematologic parameters indicating a need for treatment include at least one of the following: Hemoglobin < 11 g/dl, platelet count < 100 000/μl, absolute neutrophil count < 1000/μl. Symptomatic splenomegaly may serve as an indication for treatment.
4.1 | PNA: A standard option in symptomatic and early HCL without active infection

PNAs are the mainstay of HCL for physically fit and symptomatic HCL patients, conferring in most cases a long overall survival (OS) in first line. Either cladribine (CDA) or pentostatin (DCF) remains the standard first-line treatment. No randomized trials have compared both drugs and there is no evidence to date in the literature proving the superiority of one drug over the other. In a large representative US database including 749 HCL patients, cladribine was utilized in more than 75% of patients requiring first-line treatment.63 In large retrospective series64–68 including both agents, 76%–83% of patients receiving chemotherapy achieved complete response (CR) and 31%–33% partial response (PR), with no significant difference in CR or PR observed between both agents.

Infection is a frequent complication of HCL because of monocytopenia, neutropenia, and altered T-cell function. In addition, therapy with PNAs increases the risk of myelosuppression and infection with common pathogens and opportunistic infections (OI). PNA therapy is effective but associated with significant toxicities that increase cost.69

Recent data suggest that adding rituximab (R) to CDA has been recently proven to have therapeutic activity and could improve the duration of the CR.70 Chemo-immunotherapy associating CDA followed by R 1 month later weekly for 8 weeks was introduced in early HCL in order to achieve negative minimal residual disease (MRD) and get durable CR in untreated patients.71 In a phase II clinical trial enrolling 80 patients (59 untreated patients), CR rate was 100% demonstrating a high efficacy of chemo-immunotherapy in front-line therapy. Five-year failure-free survival (FFS) and OS were 94.8% and 96.8%, respectively. The regimen was well tolerated, with no severe or unexpected toxicity. In a randomized study, 68 patients received CDA with eight weekly doses of R.72 The first group received R treatment on day 1 (CDAR) and the second started R later at 6 months after CDA (CDA). At 6 months, the CR rate was 100% for CDAR versus 88% for CDA. The CR rate with undetectable MRD was significantly different: 97% and 24%, respectively. In addition, at 96 months median follow-up, the MRD-free rate was 94% for CDAR and only 12% for CDA, suggesting that CDAR is a very effective in first-line therapy.

4.2 | Special cases

One of the most challenging clinical situations involves the patient with symptomatic HCL and febrile infection. Attempts to control the infection should be pursued prior to instituting the PNA. If it is not possible to control the infection73 or in the event of a health crisis (Sars-Cov-2),74 the use of alpha-interferon (IFN) or vemurafenib as bridging therapy could be required transiently. Note that the use of IFN, a possible alternative in pregnant women, becomes more and more difficult due to a production stop by the laboratories.

4.3 | Second line treatment

All the published data suggest there is no long-term follow-up showing plateau in FFS. In the long term, about half of patient relapse in the first 5 years after first-line treatment. In patients who relapse, therapeutic options will depend on the first-line treatment and the duration of first remission. Patients relapsing after first-line treatment with PNAs in monotherapy are more difficult to treat and are at high risk to have a significant and impaired reduced OS.66,75 No significant difference in terms of CR or relapse free survival (RFS) was observed between patients who remained on their initial PNA or those who switched treatments.64,66

Patients treated in first-line with chemotherapy derive benefit from immuno-chemotherapy. In 14 relapsed HCL treated by CDA followed by R, CR was obtained in 100% of cases. Five-year FFS and OS was 100%. In a retrospective study including 18 pts, 12 patients treated with DCF and 6 with CDA combined to R.76 R was heterogeneously administered, with 14 patients receiving R concurrently with PNA while 4 patients received it 1–2 months after the completion of PNA treatment. All 18 patients responded to therapy, 16 patients with a CR and 2 patients with a PR. After a median follow-up of 36 months (5–83), all 16 complete responder patients remained in CR. The 13 patients, who were assessed for MRD were MRD negative. The estimated recurrence rate at 3 years after the combination treatment was 7%. Despite the small number of patients, no difference was identified between DCF and CDA.

For patients treated in first-line by chemo-immunotherapy and with a remission over 2 years, PNAs plus R as salvage therapy can be effective again as second-line therapy. In case of relapse occurring before 2 years, HCL diagnosis has to be confirmed and risk factors evaluated.77 Patients should be considered as relapsed/refractory HCL patients. The combination of bendamustine (B) with R could be an option. Twelve HCL patients received B at dose 70 mg/m2 (six patients) or 90 mg/m2 (six patients) days 1 and 2 for 6 cycles at 4-week intervals with R 375 mg/m2 days 1 and 15. Overall response rate (ORR) was 100% with 3 and 4 CR in each subgroup, MRD was undetectable in 67 and 100% of CRs, respectively, and all 6 patients without MRD remain in CR at 30 to 35 months of follow-up.78,79

4.4 | Relapsed/refractory HCL patients

The most promising and novel therapeutic options for relapsed/refractory and multiply relapsed HCL patients include BRAF inhibitors (BRAFI), recombinant immunoconjugates targeting CD22 and Bruton Tyrosine Kinase inhibitors (BTKi).

4.5 | Specific inhibitors targeting the BRAF pathway

Vemurafenib monotherapy has demonstrated significant activity in patients with melanoma and subsequently in BRAFV600E-positive
cancers including HCL patients. The optimal dose and the duration of treatment remain to be determined. The treatments are effective, with CR in 40% of cases with high dose (960 mg BID), low dose (240 mg BID), and in real life. Safety data from the clinical trials either with vemurafenib include as adverse events (AES) and serious adverse events (SAES) skin toxicity (rash, hyperkeratosis, photosensibility, kerato-acanthomas and cutaneous small cell carcinoma), ocular toxicity including central retinopathy and retinal vein occlusion, cardiac toxicity (QTc interval prolongation), elevation of AST, ALT, and serum bilirubin. All of these AES or SAES require a careful monitoring and a control of risk factors.

The use of dabrafenib monotherapy, another BRAFi, (150 mg b.i.d. for 8 weeks followed by an additional 4 weeks in patients without CR was evaluated in 10 patients). The OR was 80% including 3 CR (30%) without MRD negativity. At a median of follow-up of 64 months, OS was 90%. Dabrafenib was combined to trametinib (2 mg once daily), a MEK inhibitor. The OR was 78% including 49% CR. However, MRD negativity was only achieved in only 34% of patients in CR. The safety profile appears identical to those observed with vemurafenib.

A progression that was related to RAS mutations of chronic myelomonocytic leukemia, monoclonal B-cell lymphocytosis and acute myeloid leukemia (AML) was reported after the initiation of vemurafenib therapy. A progression of CLL was recently observed in the absence of mutations in RAS. Taken together, these data require a careful monitoring of patients treated with BRAFi.

The association of high dose vemurafenib (960 mg b.i.d.) for 8 weeks plus concomitant R: 375 mg/m² every 2 weeks then continued as consolidation four times every 2 weeks post vemurafenib has recently been proven to have a drastic therapeutic activity in HCL patients with relapsed or refractory disease. In this phase-2 trial including 30 patients, a CR was achieved in 87% evaluable patients (26 patients), a rate twice as high as that obtained with vemurafenib monotherapy. PFS was 78% at a median follow-up of 37 months and the median RFS in the 26 patients with response was 85% at a median follow-up of 34 months. MRD negativity and no previous exposure to BRAFi was associated with longer RFS. The profile of toxicity was similar to that observed with both drugs. The Scheme VR was used after moxetumomab pasudotox and the treatment was well tolerated. The novel humanized, glycoengineered Type II (obinutuzumab) or the second-generation anti-CD20 monoclonal antibodies (ofatumumab) could bring benefit in terms of response.

4.6 | Immunotoxins

The immunotoxins, fusion of a bacterial toxin to the variable region of a monoclonal antibody that is directed against a specific cell surface target such as CD22 in HCL, represent a new therapeutic option, now available in HCL patients, with or without BRAF V600E or patients with HCL variants. The preliminary results obtained with moxetumomab pasudotox (HA22, CAT-8015) are promising in a phase 1 clinical trial in relapsed HCL patients, with an ORR of 91%, including 59% of CR and no dose limiting toxicity. The maximum tolerated dose was not established. However, capillary leak syndrome and thrombotic microangiopathy can occur and have to require a careful monitoring. The pivotal, multicenter, single-arm study with moxetumomab pasudotox included a total of 80 patients with relapsed/ refractory HCL who had ≥ 2 prior systemic therapies, including ≥ 1 purine nucleoside analog. Patients received moxetumomab pasudotox 40 µg/kg intravenously on days 1, 3, and 5 every 28 days for ≤ 6 cycles. Blinded independent central review determined disease response and MRD status. Among 80 patients (79% males; median age, 60.0 years), durable CR rate was 30%, CR rate was 41%, and objective response rate (CR and PR) was 75%; 64 patients (80%) achieved hematologic remission. Among complete responders, 27 (85%) achieved MRD negativity by immunohistochemistry. The most frequent AES were peripheral edema (39%), nausea (35%), fatigue (34%), and headache (33%). Treatment-related serious AEs of hemolytic uremic syndrome (7.5%) and capillary leak syndrome (CLS) (5%) were reversible and generally manageable with supportive care and treatment discontinuation (7.5%). Moxetumomab pasudotox as re-treatment also was effective. Note that it should be difficult to obtain the drug due to a development stop.

4.7 | Bruton Tyrosine Kinase inhibitors

A multicenter phase 2 study evaluated ibrutinib, a first-in-class oral inhibitor of the Bruton tyrosine kinase, in 37 patients either with HCL (n = 28) or HCL-V (n = 9 patients) at a dose of 420 mg (24 patients) or 840 mg (13 patients). The ORR was 24% at 32 weeks and increased to 54% with 7 patients in CR (19%). PFS and OS were 73% and 85%, respectively, at 36 months. Common AES were identical to those observed in CLL.

4.8 | Bcl-2 inhibitors

Venetoclax is a selective oral small-molecule inhibitor of B-cell lymphoma-2 (Bcl-2) that restores apoptosis in cancer cells and is currently approved for the treatment of CLL and acute myeloid leukemia (AML) in adult patient ineligible for intensive chemotherapy. It also appears a very potent novel drug for the treatment of HCL and HCL-V. Recent data suggest that clinically relevant concentrations of venetoclax can induce primary HCL cell apoptosis in vitro. A decreased level of venetoclax-induced cytotoxicity in HCL cells exposed for 48 h to different stimuli (activated T lymphocytes, stromal cells, TLR-9 agonist CpG, TLR-2 agonist PAM3) was also demonstrated, suggesting that the combination of venetoclax with drugs that target the microenvironment might improve its efficacy.

4.9 | Assessment of response

CR is defined by near normalization of peripheral blood counts, resolution of palpable splenomegaly, and disappearance of hairy cells from...
the bone marrow. Bone marrow biopsy should be delayed 4–6 months after cladribine administration and performed after a clinical response with pentostatin therapy. The criteria for defining CR introduced CR with or without MRD. PR, stable disease (SD), and progression are also defined in the guidelines. The use of VE1 antibody, specific to BRAFV600E, mutated cells, could also represent a simple and first approach in clinical practice to detect MRD as well as other immunohistochemical assessment of the percentage of MRD. Flow cytometry, using an 8-color panel (CD103/CD305/CD19/CD123/CD25/CD3/CD45/CD20) can be a useful and sensitive tool for detecting MRD in the blood and/or bone marrow as well as molecular methods such as allele-specific polymerase chain reaction or next-generation sequencing. It is important to harmonize all the biologic procedures and also establish national and international networks in order to facilitate access to molecular platforms and to set up quality certificates to guarantee safe and high-quality care specific to unmutated IGHV4-34 HCL and HCL-like disorders. The clinical impact to investigate MRD is now well established, with a high risk of relapse in patients with positive testing for MRD and a low risk in patients with negative testing.

4.10 Focus on treatment of HCL-like disorders: HCL-V and SDRPL

There is no established consensus concerning the treatment of HCL-V. First-line option relies on the association of CDA with R, combined or with a sequential scheme. The same scheme could be followed in case of relapse. Ibrutinib could represent an alternative therapy either at first-line and relapse. A clinical case report also demonstrated the interest of venetoclax in a biclonal HCL-V associated with CLL. SDRPL should be distinguished from HCL-V by performing splenectomy. Treatment of SDRPL has no consensus but splenectomy with or without chemotherapy should be considered. Due to the implication of CCND3 in the pathogenesis of SDRPL, cell cycle inhibitors, such as CDK4/6 inhibitors, could also be interesting as future alternative therapeutic options.

5 EVALUATION OF SECONDARY CANCER RISK

Patients with HCL are at risk of second malignancies. The long-term OS of patients with HCL must be considered and the drugs we use must be safe and nontoxic. The occurrence of secondary cancers in HCL patients is a subject of debate. Data from worldwide cancer registries and studies tend to demonstrate an increased incidence of secondary cancers, especially hematological malignancies, with cumulative incidence varying from 5% to 32%, probably depending on the time of follow-up. Observed-to-Expected Ratio (OER) of second malignancies is usually increased: 1.01 (CI95%: 0.74–1.33), 1.2 (95% CI: 1.1–1.4), 1.65 (95% CI: 1.40–1.93), 1.86 (95% CI: 1.34–2.51), 1.88 (95% CI:1.24–2.74) or 2.6 (90% CI: 1.82–3.61). The excess incidence of second malignancies concerns hematological malignancies: 5.32 (95% CI: 2.90–8.92), particularly non-Hodgkin lymphomas: 5.03 with 95% CI from 3.77 to 6.58, 5.3 with 95% CI from 1.9 to 11.5 and Hodgkin lymphomas (6.61, 95% CI 2.13–15.42). The increased risk can be related to the disease and/or the treatment and the respective role of pentostatin or cladribine in the development of secondary malignancies remains debatable.

6 FUTURE DIRECTIONS AND CLINICAL TRIALS

The state-of-the-art changes very quickly with newly developments in diagnosis and treatment of HCL and its variants. In the coming years, we have to coordinate and standardize the procedures for MRD assessment, as was done in CLL. Efforts are needed to improve the understanding of HCL-V and SDRPL and to clarify the different clinical and/or biological criteria between both entities. Inclusion of HCL patients in clinical trials should be recommended for testing the place of new drugs in HCL: Anti-CD20 monoclonal antibodies such as obinutuzumab, new MEKi such as binimetinib and also comparing high effective associations: Vemurafenib plus rituximab versus cladribine plus rituximab. The data in real life are also crucial and the development of HCL patient data registry is required.

7 CONCLUSION

New opportunities have emerged in recent years, leading to a better understanding of HCL and a better management of HCL patients. Gray areas do exist and variants of typical HCL should be discussed in a few cases, particularly HCL-V, SDRPL or positive or negative BRAF, IGHV4-34 positive HCL. BRAF mutations are present in HCL and were also identified in HSC. Conversely, MAP2K1 mutations were detected in HCL-V. These crucial data impact the management of HCL patients: We have to discuss in patients with relapsed/refractory HCL-specific inhibitors targeting the BRAF pathway or immunotoxins. Moreover, cell cycle inhibitors or other targeted therapy could represent new perspectives in the treatment of HCL-V. The inclusion of these patients in a clinical trial should be promoted in all cases.

CONFLICT OF INTEREST

Xavier Troussard: Consultant for Innate Pharma, AstraZeneca, Abbvie. Elsa Maître and Edouard Cornet: No disclosure.

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