BHS guidelines for the diagnosis and the treatment of hairy cell leukaemia

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*On behalf of the BHS Lymphoproliferative Working Party**

SUMMARY

Hairy cell leukaemia is a rare chronic B-cell lymphoproliferative disorder characterised by a long natural course with, in most of cases, an excellent response to a single course of purine analogue monochemotherapy. Making the right diagnosis, excluding the chemo resistant variant form of hairy cell leukaemia, and making progresses in the treatment of relapsing and/or refractory disease remains challenging up to date. In recent years, exciting results with new agents are emerging and clinical trials are ongoing to optimize the management of hairy cell leukaemia and its variant form.

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INTRODUCTION

Hairy cell leukaemia (HCL) is a rare chronic B cell lymphoproliferative disorder that represents 2% of adult leukaemia's and 8% of mature B and T lymphoproliferative disorders. Median age at diagnosis is 52 years with a male to female ratio of 4:1.[1] The occurrence of familial forms of the disease suggests a genetic predisposition in some cases.[2] The role of environmental factors such as insecticides remains unclear.

CLINICAL PRESENTATION

Some patients are totally asymptomatic and the diagnosis is an accidental finding. Other patients may present symptoms related to splenomegaly or cytopenia, as infections and asthenia. Splenomegaly is present in 70-90% of cases while anemia, neutropenia and thrombocytopenia are found respectively at a frequency of 70%, 75% and 80%. Monocytopenia is characteristic of the disease and is observed in 90% of cases.[3,4]

DIAGNOSIS

Hairy cells (HCs) in the peripheral blood are found in almost 95% of cases. Morphology and flow cytometry suggest the diagnosis but a bone marrow trephine biopsy is required for confirmation.[4]

MORPHOLOGY AND FLOW CYTOMETRY

Morphologically the leukemic cells are twice as large as normal lymphocytes and show an abundant basophilic cytoplasm with projections distributed around the entire cell. They have a round kidney shaped nucleus (*Figure 1*). Monocytopenia is almost always present as well as other cytopenias.

Flow cytometry is used to detect and confirm HCs in peripheral blood or in the bone marrow aspiration: HC express the B cell lineage panel (CD19-CD20-CD22 and surface membrane immunoglobulin) but also 4 specific markers: CD11c, CD25, CD103 and CD123. These 4 markers define

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the HCL score: one point is given for each marker and a score of 3 to 4 is observed in 98% of HCL cases.[5]

When HCL is suspected but the bone marrow aspiration gives a dry tab due to fibrosis, a bone marrow biopsy is required. The HC infiltration may be patchy and thus missed in small specimens. Although the marrow is rich in most patients, 10-20% of cases show hypo cellularity that may suggest aplasia.[6] Immunohistochemistry for CD20, DBA.44 (CD72) and Tartrate-resistant acid phosphatase (TRAP) is helpful for the diagnosis and Cyclin D1 can be positive in 50% of cases.[3,7]

CYTOGENETIC AND MOLECULAR BIOLOGY

Most cases show mutations in the immunoglobulin heavy chain variable genes (*IGHV*). Patients with the unmutated form (10%) are poor responders to treatment with single agent purine analogues and have a shorter overall survival (OS).[8] The molecular variant IGHV4-34 is more common in the variant form of HCL (v-HCL) but may also occur in a small percentage of classical cases, where it also confers a worse prognosis.[8]

In 2011, Tiacci *et al*. reported the presence of the V600E mutation in exon 15 (and more rarely in exon 11) of the *BRAF* gene.[9] This *BRAF* mutation leads to the activation of the RAF/MEK-ERK pathway resulting in cell proliferation and survival.

A *BRAF* mutation is found in almost 80-100% of patients with classical HCL. It can be routinely detected by quantitative Polymerase Chain Reaction (q-PCR) or Next Generation Sequencing (NGS), two techniques with a good negative predictive value.[4,10] Recurrent chromosomal translocations are rare in HCL and the genomic profile is generally stable.[11]

IMAGING

Ultrasonography or CT-scan can be performed to check for hepato- and splenomegaly, which is generally present. Enlarged lymphadenopathies are seen in only 10% of cases.

DIFFERENTIAL DIAGNOSIS

Variant form of Hairy Cell Leukaemia (v-HCL) and Splenic red pulp Small B cell Lymphoma (SRPL) are the two entities that need to be distinguished from HCL (*Table 1*).[12]

VARIANT FORM OF HCL (V-HCL)

v-HCL is a rare entity that represents 10% of all HCL cases. This disorder must be dissociated from the classical HCL especially because of its different molecular signature and the poor clinical outcome of patients with c-HCL. It mainly affects old men with a median age of 71 years. Leucocytosis

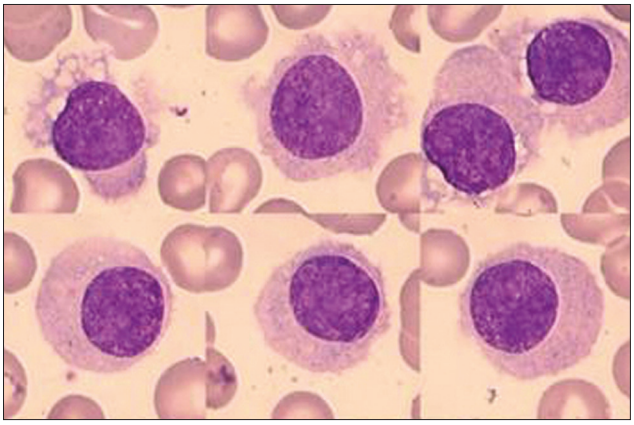

FIGURE 1. Morphology of hairy cells (*from Jolimont Hospital Laboratory of Hematology*).

is generally high in more than 90 % of cases. Monocytopenia is absent. The HCL score is low with strong expression of CD11c and CD103 but weak CD25. The *BRAF* mutation is also absent, while *TP53* mutations can frequently be detected.[13] The *IGHV* is more frequently unmutated with the IGHV4-34 rearrangement. In addition to this, there is a high prevalence of Mitogen-activated protein kinase 1 (*MAP2K1*) mutations in this patient population.[14]

SPLENIC RED PULP SMALL B CELL LYMPHOMA (SRPL)

SPRL is a rare entity that has recently been included in the updated WHO classification.[15] It affects men (sex ration, 1, 64) with a median age of 77 years and is characterized by a lymphocytosis with a heterogeneous phenotype close to v-HCL with a weak CD25, and a strong CD11c expression. The karyotype frequently reveals a 7q deletion. *BRAF* mutations are absent. There is no clear therapeutic recommendation for these patients but the clinical course is generally indolent. Usually SPRL patients do not receive treatment or they can be managed with splenectomy. In rare cases rarely cytotoxic chemotherapy with or without rituximab is used.[3,16]

DIAGNOSTIC RECOMMENDATIONS

- Complete blood count and morphology of the blood smear
- Flow cytometry Pane: B cell panel, CD25, CD11c, CD103 and CD123
- Bone marrow aspiration and biopsy
- Chest and abdominal imaging
- *BRAF*^{V600E} mutation by q-PCR
- Mutational status *IGVH* and expression of IGHV4-34 (at relapse)
- *TP53* mutation (at relapse)

TREATMENT

PROGNOSTIC FACTORS

Different clinical variables have been associated with a worse prognosis in terms of event free survival (EFS) and overall response rate (ORR): the degree of cytopenia (haemoglobin below 10 g/dl or platelet less than 100.10^9/l), presence of lymphadenopathy, absence of complete remission (CR) post treatment, an unmutated *IGHV* profile and IGVH4-34 variant, and the presence of a *TP53* mutation.

However, these parameters do not affect the first-line treatment choice, which is based on Purine Nucleoside Analogues (PNA).[17-19]

TREATMENT INDICATIONS

Indications for treatment are symptomatic splenomegaly, presence of cytopenia (haemoglobin <10g/dl, platelets $<100.10^9$/L, neutrophils $<1.10^9$/L) and recurrent or severe infections. According to some experts, severe monocytopenia could be an indication for early treatment, even in asymptomatic patients, because of a high risk of opportunistic infections.[3,4]

In the absence of treatment indications (10% of patients), clinical status and blood analysis should be re-evaluated every three months during the first year of diagnosis and every six months thereafter.

FIRST-LINE TREATMENT

The first-line treatment for HCL is based on PNA monotherapy (cladribine and pentostatin). Both agents induce a CR in a high proportion of cases (75-90%). For most patients, a CR is followed by a disease-free survival (DFS) of more than ten years in clinical studies.[4,19-21]

Cladribine (2-CDA)

Cladribine is the most commonly used drug for the treatment of HCL, with alternative routes and schedules of administration. There has been no randomised trial comparing intravenous (IV) versus subcutaneous (SC) administrations but the complete and overall response rates are similar for both routes and schedules. There is no difference in the incidence of infectious complications or haematological toxicities. The subcutaneous daily (0.14 mg/kg/d during 5 days) and the 2-hour intravenous infusion (0.14 mg/kg/d during 5 days) are the preferred schedules to allow for outpatient care. Another possibility is continuous IV infusion (0.1 mg/kg/d) for seven days.

In patients with a partial response (PR) at 4-6 months after the first treatment, a second course of PNA should be given to achieve CR with or without rituximab (not reimbursed in Belgium).[20]

Pentostatin

Pentostatin is usually given at the dose of 4 mg/m^2 IV every 2 weeks until CR, plus one or two consolidation courses. CR is generally reached after 8-10 cycles. The renal function must be normal (creatinine clearance more than 60 ml/min) and should be re-evaluated before each treatment cycle. There is no randomised clinical trial (RCT) comparing cladribine and pentostatin, but efficacy data suggest similar results.[19]

Rituximab

Rituximab can be administrated safely and successfully in combination with PNA as first-line therapy with a deeper response in term of minimal residual disease (MRD). However, long-term follow up is necessary to determine whether this combination leads to an improvement in DFS and overall survival (OS). It is generally given at the dose of 375 mg/m^2 for a total of 8 weekly administrations, starting 4 weeks after the end of cladribine.

In v-HCL and in HCL patients with unmutated *IGHV*, the combination rituximab/PNA is associated with a higher CR rate than PNA monotherapy.[22]

Interferon alpha

IFN-α still has a place in the treatment of pregnant patients and in patients with severe neutropenia (neutrophils $< 0{,}2.10^9$/L) and/or uncontrolled active infection.[17,18] The recommended dose is three million units three times/week. An alternative treatment option for patients with uncontrolled infection consists of rituximab monotherapy.

Splenectomy

Indications for splenectomy have changed since PNA therapy entered clinical practice. A huge splenomegaly (more than 10 cm under costal margin) in the presence of low-level bone marrow infiltration is still a considerable indication with long lasting remissions.[17] It can also be an option for pregnant patients.

Response evaluation

Response evaluation must be performed at least four to six months after treatment. The evaluation consists of a complete blood count, a bone marrow evaluation (aspirate with flow cytometry and biopsy), and imaging (if aberrant at diagnosis). The definition of CR includes normalisation of the peripheral blood count with no circulating hairy cells, absence of organomegaly, and the absence of HCs at immunochemistry staining of the bone marrow biopsy (Very Good Response if biopsy is not performed).[18,23]

CR with MRD negativity leads to a longer remission and is

TABLE 1. HCL differential diagnosis.

Characteristic findings	HCL	V-HCL	SRPL
Clinical features	Median age 52 years Men > women	Median age 71 years Men > women	Median age 77 years Men > women
	Indolent	Refractory to treatment	Indolent
	Splenomegaly, Monocytopenia	Splenomegaly No monocytopenia	Splenomegaly No monocytopenia
	Frequent leukopenia/ cytopenia	High lymphocytosis	High lymphocytosis
Morphology	Large lymphocyte	Medium lymphocyte	Large lymphocyte
	Abundant cytoplasm Characteristic projections	Abundant cytoplasm with some hairy projections	Abundant basophilic cytoplasm with polar villi
	Kidney shaped nucleus	Round nucleus with a pro- minent nucleolus	
Bone marrow biopsy	Fibrosis Dry tap frequent Annexin A1+	Mild fibrosis Aspiration + Annexin A1-	Mild fibrosis Aspiration+ Annexin A1-
Immunophenotype	CD19+ CD20+ CD22+	CD19+ CD20+ CD22+	CD19+ CD20+ CD22+
	CD11C+++ CD103+++ CD25++++ (CD123+)	CD11c +++ CD103 ++ CD25 -	CD11c ++ CD103 + CD25 +
HCL Score	3-4/4	0-2/4	0-2/4
Cyclin D1 expression	+ (50%)	–	–
Molecular biology/ cytogenetic	*BRAF*^{V600} (80-100%) *IGHV* mutated IGHV4-34 rarely No recurrent abnormality	No *BRAF* mutation *IGHV* unmutated IGHV4-34 frequent *MAP2K1* mutation + *TP53* mutation, del(17p)	No *BRAF* mutation *IGHV* mutated del(7q)

defined by immunohistochemical and flow cytometry techniques. However, the precise role of the MRD analysis in routine practice is unclear and there is no consensus regarding the clinical significance of MRD detection in HCL.[23]

A partial response (PR) is defined by a normal peripheral blood count, regression of organomegaly with at least 50% and the presence of residual HCs in marrow or blood.

Supportive treatment

Patients treated with PNA should receive irradiated blood components to prevent transfusion-associated graft-versus-host disease.[24]

Prophylactic treatment against herpes reactivation and pneumocystis infections are also required. Cotrimoxazole (or pentamidin aerosol) and acyclovir should be started preferably one week after the end of cladribine (to differentiate rash due to cladribine or cotrimoxazole). Both treatment should be continued until the increase of lymphocytes count above 1 x10^9/L or CD4 > 0.2 x10^9/L.[25]

Myeloid and erythroid growth factors can be used according the Belgian reimbursement criteria but are not recommended as prophylaxis.

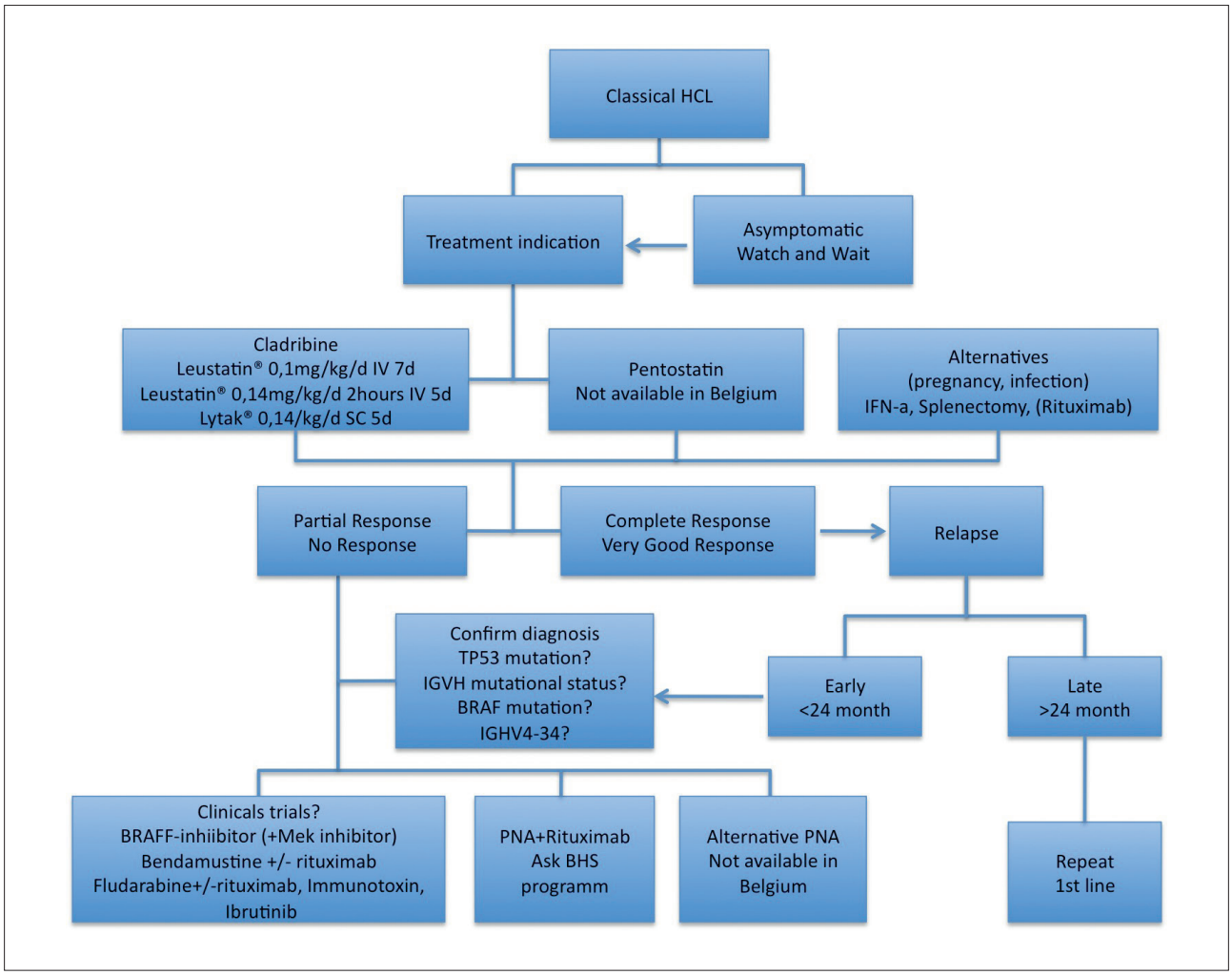

FIGURE 2. Treatment recommendations.

RELAPSE/REFRACTORY DISEASES

The choice of second-line treatment depends on the duration of response to the first-line treatment.

In case of a late relapse (i.e. after 2 years of remission), patients can be retreated with the same agent. This treatment is still effective as second- and third-line therapy in the majority of patients.[3,4] However, the CR rate and the median duration of response tend to be lower with each line of therapy.[19,21,26]

In patients with an early relapse (i.e. within two years), the alternative PNA (alone or in combination with rituximab) can be used if available and after exclusion of v-HCL, IGHV4-34 variant or a *TP53* mutation. The association between PNA and rituximab (6-8 administrations weekly) concurrently or sequentially can improve the CR rate in heavily pre-treated patients.[19,21,26,27] More studies are however needed to confirm these results.

Bendamustine-rituximab (Bendamustine 70-90 mg/m^2 day 1 - rituximab, 375 mg/m^2 day 1 and 15, 6 cycles, every 4 weeks) in repeated-relapses HCL show an ORR of 100% with a CR of 50-60%.[28] Fludarabine and rituximab (fludarabine 40 mg/m^2 orally day 1 to 5 adapted to the renal function and rituximab, 375 mg/m^2 on day 1 every four weeks for four cycles) is also effective as shown in a small retrospective study.[29]

Other treatment options, including novel agents and combination regimens are currently under clinical evaluation for the treatment of patients who are refractory/relapsing after PNA and rituximab. The oral BRAF inhibitor, vemurafenib, has been tested in a double American and Italian cohort with promising responses and an acceptable tolerability.[30] The ORR reached 96-100% with a CR rate around 35 and 42%. Unfortunately, the duration of the response was short and relapses were frequent. An ongoing study evaluating the combination of vemurafenib with rituximab shows faster and higher CR rates (86%).[31] To avoid the emergence of resistance related to *NRAS* mutations, a phase II study currently investigates the combination of a BRAF inhibitor, (dabrafenib), with a MEK inhibitor (trametinib).[23]

KEY MESSAGES FOR CLINICAL PRACTICE

1. Diagnosis is made by flow cytometry (HCL score), bone marrow biopsy and molecular biology with the detection of the *BRAF*^{V600E} mutation (q-PCR).
2. First line treatment of classical HCL is based on PNA monotherapy (only cladribine available in Belgium) (different administration routes and schedules with same efficacy and tolerability). Response evaluation must be performed 4-6 months after therapy.
3. Splenectomy or IFNa stay a valuable option in particular cases.
4. In patients with an early relapse, or in not-responding patients. The *TP53* and *IGHV* mutational status should be assessed.
5. In early relapsers (<2 years) a treatment combination including rituximab and a PNA, bendamustin, or fludarabine must be considered.
6. Patients with a late relapse (>2 years) can be retreated with the same agent.
7. Novel agents including ibrutinib, BRAF inhibitors (with or without a MEK inhibitor) and recombinant immunotoxins are promising in refractory/relapsing patients.

Recombinant immunotoxins

The Moxetumomab pasudotox is a recombinant immunotoxin composed of an anti-CD22 monoclonal antibody fused with the Pseudomonas exotoxin A. After fixation on the HC, the toxin is internalized and induces cell death. This immunotoxin has been tested in a phase I/II study in relapsing HCL patients and shows impressive results with an ORR 88% and CR rate of 64% in 33 patients. The treatment was well tolerated but two patients developed reversible haemolytic uremic syndrome. The results of the phase III study are awaited.[32] This treatment could be an interesting alternative for v-HCL patients without *BRAF* mutations who are not responding to BRAF inhibitors.

Bruton tyrosin kinase inhibitors

As shown in the preliminary results of an ongoing phase II study, ibrutinib can induce remissions in both classical HCL and in v-HCL, including relapsed and refractory patients. Moreover, the drug is associated with a good safety profile. CRs is not observed in the v-HCL patients but only in the classical form.[33] Finally, an allogenic stem cell transplantation can also be a treatment option (*Figure 2*).[34]

CONCLUSIONS

HCL is a rare B cell lymphoproliferative entity with an exceptionally long-term natural course in most patients. The treatment of HCL is based on PNA monotherapy. For non-responders or for patients with v-HCL, other therapeutic strategies are required to improve the disease outcome. One of these strategies consists of the association of PNA and rituximab. Other novel agents are promising in this setting. Clinical trials are needed to confirm these results.

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