Lancashire and South Cumbria Haematology CRG

GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF HAIRY CELL LEUKAEMIA (HCL) AND HCL VARIANT (HCL-V)

Introduction:

Hairy cell leukaemia (HCL) is an uncommon chronic B cell lymphoproliferative disorder characterized by the accumulation of small mature B cell lymphoid cells with abundant cytoplasm and “hairy” projections within the peripheral blood, bone marrow and splenic red pulp.

HCL variant (HCL-V) is classified among the unclassifiable splenic B-cell leukaemia/lymphoma that is no longer biologically related to classical HCL. It is included in the World Health Organization (WHO) classification as a provisional entity. HCL-V is an uncommon disorder, accounting for approximately 0.4% of chronic lymphoid malignancies and 10% of all HCL cases, without sexual predominance. The median age of the patients is 71 years.

BRAF V600E mutation, present in virtually 100% of cases of classical HCL, is regarded as a disease-defining event, and is absent in HCL-V.

Presentation: Presents with symptoms relating to splenomegaly or cytopenias. 60 – 80% of patients present with pancytopenia.

Physical examination reveals palpable splenomegaly in 80 – 90% of cases. Hepatomegaly and lymphadenopathy are only present in 20 and 10% of patients respectively.

Investigations

Blood film, Bone marrow aspirate, cell markers, molecular genetics, trephine and peripheral blood sample (EDTA) to be sent to HMDS Leeds.

Need for diagnostic or therapeutic splenectomy is infrequent.

Approximately 9% of patients have abdominal lymphadenopathy at presentation and the incidence increases at relapse. Computerized tomography (CT) scan at presentation is not considered essential, it may provide some prognostic information.

Where adenopathy has been demonstrated, response assessments should include a repeat CT.

Differential diagnosis

	HCL	HCLv	SDRPL	SMZL
Gender M:F	4:1	M> F	1:1	1:1
Age	Median: 58 years	Middle aged- elderly	>40 years	>60 years
Cells in peripheral blood	Hairy cells with circumferential hairy projections (may be infrequent).	Hairy cells with variable cytoplasmic projections. Prominent nucleoli.	Polar cytoplasmic projections. Basophilic cytoplasm.	Villous lymphocytes with polar cytoplasmic projections.
Immunophenotype	CD20 bright+ CD103+ CD25+ CD27− CD11c+ CD123+ DBA44+ Annexin A1+ Cyclin D1+ (weak)	CD20 bright+ CD103+ CD25- CD27+ CD11c+ CD123- DBA44+ Annexin A1− Cyclin D1−	CD20 bright+ CD103−/+ CD25- CD27+ CD11c-/+ CD123- DBA44+ Annexin A1− Cyclin D1−	CD20+ CD103- CD25-/+ CD27+ CD11c+/− CD123- DBA44+ Annexin A1− Cyclin D1−
Marrow involvement	Diffuse and interstitial 'honeycomb' pattern. Minor intrasinusoidal component may be seen. Fibrosis marked.	Interstitial, rarely diffuse. Predilection to sinusoidal infiltration. Reticulin fibrosis not significant (easier to aspirate than classical HCL).	Intrasinusoidal, interstitial and nodular.	Nodular and intrasinusoidal.
Spleen histology	Red pulp infiltration with red blood cell lakes. Atrophic white pulp.	Red pulp infiltration with red blood cell lakes. Atrophic white pulp.	Diffuse red pulp involvement of cords and sinusoids. White pulp spared.	Marked expansion of white pulp and infiltration of red pulp.
Molecular genetics	*BRAF* V600E mutated in most cases.	*BRAF* V600E not mutated. *MAP2K1* mutations.	*CCND3* PEST domain mutations.	Del7q (40%), *NOTCH2* and *KLF2* mutations.

Staging

There is no widely agreed system for staging HCL. The disease affects mainly bone marrow and spleen and progresses slowly.

Management

Asymptomatic patients:

Many patients are asymptomatic and can be observed for months or years after the diagnosis is established before requiring treatment. No clear advantage to early treatment.

Complete history, physical examination, and complete blood cell count with a differential test every 3–6 months in untreated patients.

The risk of opportunistic infection in patients with monocytopenia ± neutropenia is high; even asymptomatic patients may be considered for early treatment.

Indications for Treatment:

Treatment should be initiated in patients with symptomatic disease manifested by

1. Bulky or progressive, symptomatic splenomegaly.

2. Symptomatic cytopenias
3. Constitutional symptoms.

Initial treatment:

- The purine nucleoside analogues (PAs), pentostatin and cladribine, remain the standard front-line treatment for HCL
    - Cladribine (**2-CldA**) – see network protocols. IV or SC preparations can be used.
    - Pentostatin (2'-deoxycoformycin **DCF**) - see network protocols.

With purine analogues prophylaxis with Septrin and Acyclovir is recommended. This should be continued until for up to six months post completion of therapy or until adequate neutrophil and lymphocyte recovery. In the case of Cladribine, they should be commenced after the 5-day course of treatment, since rashes can occur when the drugs are given concurrently. Allopurinol is not required. Blood transfusion after purine analogue therapy should be with irradiated blood, indefinitely. GCSF can be given but currently not recommended in the BCSH guidelines.

- Single agent Rituximab. Has not been formally tested in the first-line setting. At a dose of 375 mg/m^2 for four weeks can be considered in patients whose comorbidities preclude the use of nucleoside analogues or who present with an active infection. This treatment can also be considered in neutropenic patients due to hairy cell leukaemia in whom the inevitable worsening of cytopenias for two to four weeks post treatment is considered high risk. Example: -those presenting with intercurrent infection, those requiring intensive care or frailty. There is evidence that improved remissions may be achieved with the combination of rituximab and a PA. Definitive treatment with nucleoside analogues can be considered later.
- Interferon-α: is now rarely used, being poorly tolerated and less effective than PAs, but may occasionally still be useful in patients who present with serious infection and severe pancytopenia. It can also be used in patients presenting with very severe neutropenia (neutrophil count <0.2 × 109/l) to increase the neutrophil count prior to nucleoside analogue therapy. Also consider for treatment of HCL in pregnancy.
- Splenectomy: is rarely undertaken now, since PA therapy is effective in reducing the size of the spleen.

Response assessment:

Bone marrow aspirate, trephine, cell markers and peripheral blood (EDTA) should be assessed after count recovery; typically 4–6 months after cladribine therapy or following 8–9 courses of pentostatin or when the blood count has normalised (apart from lymphopenia), offering 2–3 further pentostatin injections if CR is demonstrated. Samples should be sent to HMDS Leeds.

A second course of purine analogue therapy is recommended if patients do not enter complete remission at this timepoint. The addition of rituximab may be considered usually given at least 6 months after the end of therapy.

1. **Complete remission:** Requires morphological absence of hairy cells in the blood and bone marrow and normalisation of any organomegaly and cytopenia.
2. **Partial response (PR):** Requires normalisation of peripheral counts, together with at least 50% reduction in organomegaly and bone marrow hairy cells and less than 5% circulating hairy cells.
3. **Non- responses (NR):** All other responses.
4. **Relapse:** Any deterioration in blood counts related to the detection of hairy cells in peripheral blood and/or bone marrow and/or increasing splenomegaly.

Eradication of minimal residual disease (MRD), in contrast to overtly persistent disease, should not be the aim of therapy except as part of a clinical trial.

Treatment of relapsed patient and patients refractory to purine analogues

- Clinical trials when possible.
- The **alternative nucleoside analogue** can be used in early relapse within 3 years after the first-line treatment or primary resistance.
- Late relapse can be effectively retreated with **2-CldA or DCF** with the addition of Rituximab (6–8 doses given concurrently or sequentially) to a PA can improve this response- see network protocols

- **Bendamustine** at 70–90 mg/m2 combined with rituximab is another therapeutic option in multiply relapsed/refractory HCL, and could be considered in HCL patients after the failure of standard therapies
- **Interferon Alpha** can be considered although complete remissions are uncommon. Treatment with interferon alpha is now rarely used but can be considered in patients failing treatment with purine analogue. This has previously been used to improve pancytopenia in patients who are unable to tolerate subsequent purine analogue therapy with fewer infectious complications but this role has now been largely superseded by **Rituximab**.
- **Moxetumomab pasudotox** is a recombinant immunotoxin directed against CD22 and linked to a truncated Pseudomonas exotoxin. CD22 is strongly expressed on hairy cells. It is not NICE approved by the time of updating this guideline.
- BRAF inhibitor **Vemurafenic** or **Dabrafenib**, via clinical trials.
- **Fludarabine in combination with rituximab** for four cycles, can be a therapeutic option in relapsed or refractory patients previously treated with 2-CldA.
- **Splenectomy**: resistant massive symptomatic splenomegaly (>10 cm below the costal margin) with accompanied low-level bone marrow infiltration. As a temporising measure in symptomatic pregnant females. Splenectomy largely obsolete and purine analogues generally obviate the need for splenectomy in most other settings.
- **Allogenic Stem Cell Transplantation:** potential role in younger, heavily pretreated HCL patients who have had multiple relapses and are refractory to purine analogues and Rituximab.

Treatment of HCL-V

There is very little specific data on the treatment of HCL-V, but it is well recognised that the response rates and duration of response to PAs is inferior to that seen in classical HCL. For this reason, it is recommended that **cladribine plus rituximab** 6 – 8 doses be used as first-line therapy.

Moxetumumab pasudotox with less good results than seen in classical HCL.

Ibrutinib has had the same outcome as the classical HCL cases in phase II clinical trials.

BRAF inhibition is not appropriate, given that the variant cases do not harbour BRAF mutations.

Trametinib has been shown to have activity, MAP2K mutations are seen in about half the cases.

Splenectomy may be considered in refractory cases to alleviate symptoms and cytopenias. This can be followed by Rituximab therapy.

Follow-Up

A follow-up of asymptomatic patients should include a complete history, physical examination, a blood cell count and routine chemistry every 3–12 months. Monitoring for second malignancies required. Solid and haematological malignancies develop in 10% of treated or untreated patients with HCL, particularly chronic lymphoproliferative diseases (myeloma, Hodgkin's and non- Hodgkin's lymphoma), melanoma and thyroid cancer

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