Revised Guidelines for the Diagnosis and Management of Hairy Cell Leukaemia and Hairy cell Leukaemia Variant

Compiled on Behalf of the Clinical Task Force of the British Committee for Standards in Haematology as a revision to original guideline published February 2000.

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Development of the Guidelines

The guideline group was selected to be representative of UK-based medical experts. MEDLINE and EMBASE were searched systematically for publications in English from 1990 – 2010 using key words: 'hairy cell leukaemia'. The writing group produced the draft guideline which was subsequently revised with consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH and the British Society for Haematology Committee and comments incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found in appendix 1. The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with hairy cell leukaemia. The guidance may not be appropriate to every patient with hairy cell leukaemia and in all cases individual patient circumstances may dictate an alternative approach.

Major changes since last guideline

These guidelines represent a revision of the 2000 BCSH guidelines (Catovsky 2000). The major changes outlined in this guideline are:

1. Partial response to purine analogues is now regarded as a poor prognostic factor. Bone marrow assessment after count recovery (typically 4-6 months after cladribine therapy or following 8-9 courses of pentostatin) is recommended.
2. A second course of purine analogue therapy is recommended if patients do not enter complete remission at this time-point. The addition of rituximab may be considered.
3. Rituximab in combination with a purine analogue is recommended in the treatment of relapsed disease.

Summary of key recommendations.

- **Blood film and bone marrow examination are essential for the diagnosis of hairy cell leukaemia. (Grade 1C)**
- **Flow cytometric evaluation should be undertaken when liquid material is available. CD11c, CD25, CD103 and CD123 are advised if hairy cell leukaemia is suspected. (Grade 1C)**
- **Immunohistochemistry on bone marrow trephine specimens should include CD20 and CD72 (DBA.44). (Grade 1C)**
- **CD20 is the most useful immunohistochemical stain to use when assessing remission status post-treatment. (Grade 1C)**
- **It is likely that screening for the presence of BRAF V600E mutation will be required in the near future. (Grade 2C)**
- **Occasional patients who are asymptomatic may not require immediate therapy on diagnosis; active monitoring is appropriate. (Grade 2C)**
- **Patients with symptomatic cytopenias or painful splenomegaly require therapy. (Grade 1C)**
- **Purine analogues (cladribine or pentostatin) are the most appropriate agents for first-line therapy. No difference in efficacy between these has been demonstrated. (Grade 1B)**
- **Subcutaneous cladribine administration is likely to be the most cost-effective option. (Grade 2C)**
- **Patients who have received cladribine or pentostatin should be transfused only with irradiated blood products for the rest of their lives in order to minimise the risk of transfusion-associated graft-versus-host disease. (Grade 1B)**
- **Patients who have received cladribine or pentostatin should receive aciclovir and co-trimoxazole prophylaxis for herpes infections and *Pneumocystis jiroveci* infection respectively until the lymphocyte count is ≥1 x 10^9/l. (Grade 2C)**

- **Patients who have received cladribine or pentostatin and have required treatment for herpes infections or pneumocystis should continue aciclovir or co-trimoxazole prophylaxis respectively, until the CD4 count is ≥0.2 x 10^9/l. (Grade 2C)**
- **Response to purine analogue therapy should be assessed by bone marrow examination once the blood count has recovered, typically 4-6 months after cladribine therapy or after 8-9 courses of pentostatin (Grade 1B).**
- **Residual disease should be treated using further purine analogue therapy. (Grade 2C)**
- **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. (Grade 2C)**
- **Patients who relapse after purine analogue therapy should be re-treated either with the same or the alternative purine analogue depending upon the duration of remission. The use of rituximab is recommended in this setting. (Grade 2C)**
- **Routine use of growth factors is not recommended. (Grade 2C)**
- **Splenectomy can be considered if patients have symptomatic splenomegaly, particularly if marrow involvement is minimal. (Grade 2C)**
- **It is not possible to make firm recommendations regarding the treatment of hairy cell leukaemia variant (HCL-v); additional studies are required.**
- **Splenectomy results in partial remission for some patients with HCL-v. (Grade 2C)**
- **Purine analogues +/- rituximab may benefit some patients with HCL-v. (Grade 2C)**

1. Introduction

Hairy cell leukaemia (HCL) is an uncommon B-cell lymphoproliferative disorder affecting adults. HCL was first reported as a distinct disease in 1958 (Bouroncle *et al*, 1958). The prevalence has been estimated at 2% of all forms of leukaemia and, of patients affected by lymphoproliferative diseases which comprise mature B or T cells, HCL accounts for 8% of cases. HCL is 6–10 times more rare than chronic lymphocytic leukaemia (CLL). Interest in HCL has evolved in parallel with the development of useful therapeutic agents: interferon alpha and pentostatin in the 1980s and cladribine in the 1990s. HCL affects middle-aged men more commonly than women; the male:female ratio being 4.5:1 with a median age at onset of 50 years.

2. Clinical and Laboratory Features

Patients may be asymptomatic and the disease is identified because a full blood count is taken for an unrelated reason. Other patients present with symptoms of cytopenia, particularly infections.

The most common laboratory finding is cytopenia, usually affecting two or three lineages; monocytopenia is a consistent feature. Leucocyte counts tend to be low (usually less than 5×10^9/l and very rarely over 10×10^9/l), except in the HCL-variant where the count is typically higher and monocytopenia is not a feature (see below). Hairy cells are often seen in peripheral blood films but their proportion is variable. Splenomegaly is a common finding (table 1).

2.1 Diagnostic Tests

Careful examination of peripheral blood films will show the characteristic hairy cells, which are approximately twice as large as normal lymphocytes and have a

round, oval or kidney-shaped nucleus and a loose chromatin pattern (Bennett *et al,* 1989). Bone marrow aspiration is successful in only approximately 10% of patients. The marrow films obtained may demonstrate the presence of hairy cells but definitive diagnosis usually requires a bone marrow trephine biopsy due to the high frequency of a dry tap on aspiration. Ideally a core of 2–3 cm in length should be obtained as HCL infiltration may be patchy and can be missed in small specimens. Trephine biopsy histology reveals a unique pattern of infiltration, either diffusely interstitial or focal, with cells appearing separated because of their abundant clear cytoplasm. Reticulin fibres in the background marrow stroma are diffusely increased in association with HCL infiltrates. This explains the difficulty in obtaining a good marrow aspirate and the frequent occurrence of a dry tap. Confirmation of the nature of the infiltrate is obtained by immunocytochemistry performed on paraffin sections using CD20, DBA.44 and an antibody reactive with tartrate-resistant acid phosphatase (TRAP). Expression of both TRAP and CD72 (the antigen reactive with DBA.44) has been shown to have 100% sensitivity for HCL and a high specificity for the disease; combined TRAP/DBA.44 positivity was found in only 3% of cases of non-HCL lymphoproliferative disease (Went et al, 2005). Monoclonal CD11c, CD25 and CD123 antibodies are now available for use with paraffin-embedded tissue sections but annexin A1 is the most specific HCL marker currently available. Annexin A1 is not expressed in any other small B-cell lymphoproliferations (Falini *et al,* 2004). Despite its specificity, annexin A1 is not useful for detecting minimal involvement at diagnosis or low levels of residual HCL after treatment as it also expressed by myeloid cells and some T cells (Foucar *et al,* 2008). It should be noted, when undertaking immunohistochemistry to support a diagnosis of HCL in trephine biopsy sections, that up to 50% of cases show nuclear positivity for cyclin D1 (Miranda *et al,* 2000). Confusion with mantle cell lymphoma is, however, extremely unlikely as the cytology and histology of mantle cell lymphoma is quite different from HCL. Neoplastic cells may also have immunohistochemically detectable CD10 expression in up to 20% of cases but

this is not associated with altered prognosis (Jasionowski *et al*, 2003; Chen *et al*, 2006).

Good quality trephine biopsy specimens are required not only for diagnosis but crucially also for assessing the response to treatment. It is notoriously difficult to detect low levels of residual HCL cells using haematoxylin-eosin stained sections alone, and the initial increase in stromal reticulin is often reversed before neoplastic cells are completely cleared. Additional immunohistochemistry for CD20 is required as a minimum. Use of DBA.44 and other more HCL-specific antibodies is not recommended unless as part of a wider panel including CD20 since their performance is inferior in this context. Clusters of positively stained cells or widely dispersed CD20-positive lymphocytes are taken as evidence of residual disease.

Demonstration of TRAP by cytochemistry has been shown to be a useful test for HCL in the past but the availability of monoclonal antibodies reactive with TRAP, which can be used successfully in bone marrow trephine sections, has largely obviated the need for the cytochemical test.

Where liquid material is available, either peripheral blood or aspirated bone marrow, flow cytometry studies can be very helpful. Markers of B cells, such as CD19, CD20 and CD22, are always positive. With a panel of five monoclonal antibodies (McAb) which define the CLL score (Moreau *et al*, 1997), HCL gives low scores (0–1) while CLL scores 4–5. Hairy cells are CD5 and CD23 negative, express surface membrane immunoglobulin (SmIg) strongly with either κ or λ chains and are FMC7 positive. A panel of antibodies which are more specific for hairy cells should also be applied whenever this diagnosis is entertained (table 2). The HCL panel advised for flow cytometry consists of CD11c, CD25, CD103 and CD123 (Del Giudice *et al,* 2004). When 3 or 4 of these reagents are positive they allow distinction between HCL (scores 3–4) and other B-cell disorders (scores 0–1).

In exceptional cases, the diagnosis of HCL is made by histological analysis of splenic tissue after splenectomy or splenic needle core biopsy. Spleen histology shows infiltration of the red pulp with disruption of the normal architecture of cords and sinusoids, accompanied by extreme atrophy of the white pulp. This pattern is almost unique and is not seen in most other B-cell lymphoproliferative disorders, in which the white pulp is generally expanded. Exceptions are splenic diffuse red pulp B cell lymphoma, a new provisional entity in the 2008 WHO classification of lymphomas (Mollejo *et al*, 2002; Foucar *et al*, 2008) and examples of hairy cell leukaemia-variant (HCL-v) having prolymphocytic morphology (Foucar *et al,* 2008). Splenic histology can therefore confirm the diagnosis of difficult cases but splenectomy is rarely indicated solely for diagnostic purposes.

Whole exome sequencing of HCL cells in parallel with normal cells has recently revealed the presence of the *BRAF* V600E mutation in all of 47 cases of HCL tested (Tiacci *et al*, 2011). In future this finding is likely to have major implications for diagnosis, monitoring and potentially even treatment of HCL. Whilst these data have not yet been validated in an alternative data set, it is reasonable to request screening for this mutation in newly diagnosed patients (Grade 2C).

2.2 Staging and Prognostic Features

There is no widely agreed system for staging HCL. The disease affects mainly bone marrow and spleen and progresses slowly. Most prognostic features relate to the status of both organs. Heavy bone marrow infiltration and a large spleen will result in maximal degrees of cytopenia. Anaemia (< 100 g/l), neutropenia (< 1.0 x 10^9/l) and thrombocytopenia (< 100 x 10^9/l) in any combination are associated with a relatively poor prognosis (Maloisel *et al,* 2003, Else *et al,* 2009). Approximately 9% of patients have abdominal lymphadenopathy at presentation and the incidence increases at relapse. Such adenopathy has

been associated with poorer response to treatment and reduced overall survival (Mercieca *et al*, 1994 &1996). While a 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.

An assessment of prognostic factors should also include response to purine analogue therapy. Those achieving only a partial response (PR) fared significantly worse than patients achieving complete remission (CR) (Lauria *et al*, 1997; Maloisel *et al,* 2003; Else *et al,* 2009). Else et al (2009) demonstrated that the median disease free survival (DFS) for patients attaining CR was not reached after a median follow up of 20 years. In those attaining a PR, DFS was 4 years ($p<0.0001$). In multivariate analysis, response to treatment (CR versus PR) was the variable most significantly associated with improved DFS (Else *et al*, 2009; Dearden *et al*, 2011). For these reasons, aiming to achieve a CR is an important goal of treatment.

Response to splenectomy, assessed by improvement of blood counts, has also been shown to be a reliable predictor of the need for subsequent therapy. As splenectomy is not now the main treatment approach in HCL, the above considerations are valid only if splenectomy is considered necessary as part of the overall management.

Recommendations

- **Blood film and bone marrow examination are essential for the diagnosis of hairy cell leukaemia. (Grade 1C)**
- **Flow cytometric evaluation should be undertaken when liquid material is available. CD11c, CD25, CD103 and CD123 are advised if hairy cell leukaemia is suspected. (Grade 1C)**
- **Immunohistochemistry on the marrow trephine specimens should include CD20 and DBA .44. (Grade 1C)**

- **CD20 is the most useful immunohistochemical stain to use when assessing remission status post-treatment. (Grade 1C)**
- **It is likely that screening for the presence of BRAF V600E mutation will be required in the near future. (Grade 2C)**

3. Treatment

The majority of patients will require therapy to correct the cytopenias and associated problems of anaemia, infections and bleeding. If the patient is asymptomatic and cytopenias are minimal, however, it is reasonable to adopt a watch-and-wait policy. It should be noted that the risk of opportunistic infection in patients with monocytopenia +/- neutropenia is high; even asymptomatic patients may be considered for early treatment. The main indications for treatment are:
- symptomatic cytopenias
- painful splenomegaly

3.1 Purine Analogue Therapy as Primary Treatment

3.1.1 Responses to Purine Analogue Therapy

The mainstay of HCL treatment comprises the two nucleoside analogues pentostatin (Catovsky *et al*, 1994; Golomb *et al*, 1994; Grever *et al,* 1995) and cladribine (Hoffman *et al,* 1997; Lauria *et al,* 1997; Saven *et al*, 1998). Both agents induce CR in a high proportion of patients (> 80%) which, in the majority, are prolonged; median duration of DFS is in excess of 10 years in most studies (Maloisel *et al*, 2003; Zinzani *et al*, 2004 & 2010; Else *et al*, 2005 & 2009; Chadha *et al*, 2005).

Pentostatin and cladribine have not been tested against each other in large randomised trials. Most of the available response and toxicity data derive from published series (Golomb *et al,* 1994; Grever *et al*, 1995; Hoffman *et al*, 1997; Lauria *et al*, 1997; Cheson *et al,* 1998; Saven *et al*, 1998; Maloisel *et al*, 2003, Zinzani *et al*, 2004; Else *et al,* 2009). A long-term follow-up study has demonstrated no difference in outcome between the two agents (Else *et al*, 2009). In this single-institution study, median DFS was 16 years.

Since overall survival (OS) in HCL is now 95–98% at 5 years, the end-point to assess the value of any treatment in the medium or long term should be DFS, defined as time from the start of treatment until documented relapse requiring treatment, censored at the date of latest follow-up (or death from unrelated causes) in patients remaining disease free. Alternatively event-free survival (EFS) may be used, calculated until the date of a specific pre-defined event, such as >50% increase in organomegaly and/or appearance of >5% circulating hairy cells.

3.1.2 Purine Analogue Treatment Schedules

Once the diagnosis of HCL is confirmed and it has been established that intervention is indicated, treatment should be initiated with either of the purine analogues. Various treatment schedules have been tested and are outlined in Table 3. Either drug is likely to induce a CR with minimal toxicity. Median relapse-free survival in patients attaining a CR is significantly longer than in those attaining only a PR (Lauria *et al,* 1997; Maloisel *et al,* 2003; Else *et al*, 2009). For this reason treatment with either agent should be repeated until a CR results. The addition of 6-8 doses of rituximab, delivered either concurrently with or after the purine analogue (Cervetti *et al*, 2004; Ravandi *et al*, 2006; Else *et al*, 2007) may help to achieve this goal in patients requiring multiple courses of pentostatin or a second course of cladribine.

Pentostatin requires a normal creatinine clearance (> 60 ml/min) for the recommended dose but a half dose could be given if the clearance is between 40 and 60 ml/min. Anti-emetics should be given with each injection and prophylaxis with cotrimoxazole commenced when the patient becomes lymphopenic (< 1 x 10^9/l), continued for at least 6 months. Many units give a 1.5 l intravenous fluid infusion with the drug to reduce renal toxicity (Grever *et al*, 1995).

Cladribine has been delivered in a variety of ways including continuous 7 day intravenous infusion, intravenous infusion over 2 hours per day for 5 consecutive days, daily subcutaneous injection for 5 consecutive days (Juliusson *et al,* 1995) and weekly subcutaneous injection for 5 or 6 consecutive weeks. In randomised trials no difference in outcome has been shown comparing 2 hour intravenous infusions (0.12 mg/kg) for 5 consecutive days versus weekly intravenous infusions (0.12 mg/kg) for 6 consecutive weeks (Robak *et al,* 2007). Similarly no difference in outcome has been shown comparing subcutaneous injections (0.14 mg/kg) for 5 consecutive days versus weekly intravenous infusions (0.14 mg/kg) for 5 consecutive weeks (Zenhausern *et al*, 2007). It remains true that by the nature of this low grade malignancy, the long-term follow-up data mainly pertain to patients treated with a 7 day continuous intravenous infusion schedule (Chadha *et al*, 2005; Jehn *et al*, 2005; Else *et al,* 2009) as this was the first widely used cladribine protocol. Data relating to subcutaneous or intravenous bolus injection of cladribine are relatively less mature but initial responses are very similar to those seen with the continuous infusion regimen (Sperb *et al,* 1998; von Rohr *et al*, 2002; Zinzani *et al,* 2004; Robak *et al*, 2007). Pharmacological studies lend weight to this argument; bioavailability, as assessed by area-under-the-curve analysis, is very similar for administration of 0.14 mg/kg cladribine given either by subcutaneous or intravenous bolus (Liliemark *et al,* 1998).

Given the ease of delivery of daily subcutaneous cladribine compared with the other options and the reduced resource use that follow from the use of this

regimen, it is reasonable to use this as first-line therapy for patients requiring treatment. If only a PR is obtained after treatment, by this or any other modality, it is reasonable to repeat a second course of therapy.

It is recommended that the use of concomitant drugs should be minimised during cladribine infusions as patients often develop rashes. Cotrimoxazole and aciclovir should be started, once treatment is completed, to prevent pneumocystis infections and herpes reactivation respectively. Where possible, active infection should be treated prior to commencement of purine analogue therapy. Patients receiving pentostatin or cladribine should receive irradiated blood components indefinitely to prevent transfusion-associated graft-versus-host disease (Treleaven *et al*, 2011). Patients should be informed of the need for irradiated blood and given an appropriate warning card to carry. In addition a flag stating this lifelong requirement should be placed on the blood bank computer.

3.1.3 Assessment of Response to Purine Analogues

Assessment of response (PR or CR) is an important endpoint of the initial treatment. For guidance, the full blood count should have normalised (with the exception of lymphopenia which is anticipated after treatment) before a bone marrow biopsy is performed. CR is defined as the absence of hairy cells from the peripheral blood and bone marrow along with resolution of organomegaly and cytopenias. In CR immunohistochemistry reveals no clustering (≥3 cells) of CD20-positive or DBA.44-positive cells. PR is defined as a normalisation of cytopenias along with a minimum 50% improvement in both organomegaly and bone marrow infiltration with no circulating hairy cells.

After cladribine, this should be at a minimum of 4 months after the end of treatment (normally 4 or 6 months). If there is PR, with significant residual HCL, a second course of cladribine may be required to achieve CR, usually given at

least 6 months after the end of therapy. In a single centre follow-up study of 242 patients (Dearden *et al*, 2011), 18 patients treated with cladribine (12 as first-line and 6 as second-line therapy) who remained in PR after bone marrow reassessment received a repeat treatment with cladribine 4-7 months after initial treatment. This led to CR in 14 patients, of whom all but 1 remained in CR at a median follow-up of 6 years (range 1-16 years). One may consider adding rituximab to the second course of cladribine (see below). With pentostatin the practice has been to do a bone marrow biopsy after 8 – 9 courses when the full blood count has normalised (though lymphopenia will persist). If CR is documented, one or two further pentostatin injections are recommended (Else *et al,* 2009).

3.2 Treatment at Relapse

The majority of relapsed patients achieve second remission when re-treated with either pentostatin or cladribine. Choice of agent at relapse may depend on the duration of first remission: if short, i.e. < 2 years, use the alternative agent; if longer (>2 years) retreat using the same agent. The long-term follow-up study of Else *et al* (2009) demonstrated that CR was equally durable whether obtained after first-, second- or third-line therapy. However, the percentage of patients achieving CR diminishes with each round of therapy (Else *et al*, 2009; Zinzani *et al*, 2010). The combination of pentostatin or cladribine with rituximab is therefore suggested for patients who have relapsed (Else *et al*, 2009 & in press). Evidence from the few non-responders, or patients who become refractory, suggests a lack of cross-resistance between pentostatin and cladribine (Grever 2010). Both agents are well tolerated in the long term with lymphocytopenia being the main concern.

*3.*3 Minimal Residual Disease

Despite the excellent clinical responses documented with pentostatin and cladribine, there is evidence that minimal residual disease (MRD) remains after the use of either agent (Pileri *et al*, 1994; Konwalinka *et al*, 1995). More recently, two subtypes of MRD have been defined (Mhawech-Fauceglia *et al*, 2006) which correlated with relapse risk over a 55 month follow-up period. Several groups have used rituximab in combination with nucleoside analogue therapy and MRD has not been detectable by molecular or flow cytometric techniques in >90% of patients (Cervetti *et al,* 2004 & 2008; Ravandi *et al,* 2006; Else *et al*, 2007 & 2011 in press). These studies are, however, small (n=10-18). Further large-scale studies are needed to evaluate whether MRD negativity has an impact on DFS or overall survival. Sigal e*t al* (2010) have recently demonstrated that MRD may be present in long term survivors without evidence of disease progression. Eradication of MRD should not be the aim of management except as part of a clinical trial.

*3.*4 Role of Interferon alpha

Given the excellent results gained with purine analogue therapy, interferon alpha is rarely used to treat HCL. The role of interferon alpha is nowadays limited to patients who present with severe pancytopenia and for whom there is a pressing need for cell count recovery as quickly as possible. A regimen of 3 mega-units 3 times a week will gradually improve blood counts and facilitate the subsequent use of either nucleoside analogue (Dearden and Catovsky, 1990; Habermann *et al*, 1992). There is also some evidence that improvements in bone marrow function prior to pentostatin may improve long-term results (Catovsky, 1996) and decrease the number of injections required to achieve remission. Maintenance therapy is not recommended due to limited efficacy and numerous side-effects which impact adversely on quality of life.

3.5 Role of Growth Factors

G-CSF can also be used to treat severe neutropenia (< 0.5 x 10^9/l) before, during and/or after the use of either pentostatin or cladribine. The routine use of G-CSF cannot, however, be recommended. Data from a phase 2 study compared patients treated with cladribine and G-CSF with historical controls who were not given G-CSF. While G-CSF reduced the number of days of neutropenia, it did not reduce number of febrile days or antibiotic use (Saven *et al*, 1999).

3.6 Role of Splenectomy

Indications for splenectomy in HCL have changed since the advent of purine analogue therapy. The principal indication for splenectomy is very significant splenomegaly (>10 cm below costal margin) in the presence of low level bone marrow infiltration. It should not be forgotten that some patients (approximately 2% of all cases and 15% of those splenectomised because of a large spleen) may remain in clinical remission with normal blood counts for periods of 15 to 25 years. In these patients, the bone marrow does not improve but remains minimally involved and occasional circulating hairy cells are seen in blood films. It is not clear, however, whether splenectomy, undertaken as a debulking procedure, improves long-term results. If a patient is splenectomised, it is important to wait for the full benefits of splenectomy to be apparent before starting any other therapy. It is therefore recommended that at least 6 months should be allowed to pass after splenectomy before considering any other treatment. A slow rise in circulating hairy cells is a feature suggesting subsequent progression. If blood counts normalise and the patient remains asymptomatic, a decision on further treatment could safely be delayed indefinitely. With respect to prophylaxis of infection in those patients who have a splenectomy, readers are referred to the recent BCSH guidance document (www.BCSHguidelines.com).

3.7 Management of Refractory Disease

Another role for rituximab in the management of HCL is to treat patients whose disease is refractory to therapy with cladribine or pentostatin. The regimen with the best documented outcome to date is 375 mg/m^2 given weekly for 8 weeks (Nieva *et al*, 2003; Thomas *et al*, 2003). In this latter study, 12/15 patients responded with 8/12 achieving marrow morphological CR. 7/12 responders had maintained that response at 32 months. Both studies included patients who had relapsed after cladribine or pentostatin in addition to those with primary refractory disease. Although combination of rituximab with the alternative nucleoside analogue may be effective in non-responders, data are currently lacking. Studies are under way using immunotoxins directed against CD25 and CD22 (Kreitman *et al*, 2009). Further clinical studies would, of course, be essential before such agents could be incorporated into a routine treatment schedule (Grever 2010). The management of HCL is summarised in table 4.

3.8 Management of HCL in Pregnancy

Given that HCL tends to affect men more than women and typically begins later in life, the prevalence of the disease in pregnant women is extremely low. There are limited data to guide treatment definitively. It seems reasonable, as for other patients, to avoid therapy in the absence of symptoms. If treatment is required, interferon alpha would be reasonable first line treatment.

Recommendations

- **Occasional patients who are asymptomatic may not require immediate therapy on diagnosis; active monitoring is appropriate. (Grade 2C)**
- **Patients with symptomatic cytopenia or painful splenomegaly require therapy. (Grade 1C)**

- **Purine analogues (cladribine or pentostatin) are the most appropriate agents for first-line therapy. No difference in efficacy between these two agents has been demonstrated. (Grade 1B)**
- **Subcutaneous cladribine administration is likely to be the most cost-effective option. (Grade 2C)**
- **Patients who have received cladribine or pentostatin who require transfusion should be transfused only with irradiated blood products for the rest of their lives in order to minimise the risk of transfusion-associated graft-versus-host disease. (Grade 1B)**
- **Patients who have received cladribine or pentostatin should receive aciclovir and co-trimoxazole prophylaxis for herpes reactivation and pneumocystis infection, respectively, until the lymphocyte count is ≥1 x 10^9/l. (Grade 2C)**
- **Patients who have received cladribine or pentostatin and have required treatment for herpes infections or pneumocystis should continue aciclovir or co-trimoxazole prophylaxis respectively until the CD4 count is ≥0.2 x 10^9/l. (Grade 2C)**
- **Response to purine analogue therapy should be assessed by bone marrow examination once the blood count has recovered, typically 4-6 months after cladribine therapy or after 8-9 courses of pentostatin (Grade 1B).**
- **Residual disease should be treated using further purine analogue therapy. (Grade 2C)**
- **Eradication of MRD (in contrast to overtly persistent disease) should not be the aim of therapy except as part of a clinical trial. (Grade 2C)**
- **Patients who relapse after purine analogue therapy should be re-treated either with the same or the alternative purine analogue depending upon the duration of remission. The use of rituximab is recommended in this setting. (Grade 2C)**
- **Routine use of growth factors is not recommended. (Grade 2C)**

- **Splenectomy can be considered if patients have symptomatic splenomegaly, particularly if marrow involvement is minimal. (Grade 2C)**

4. Hairy Cell Leukaemia-variant (HCL-v)

Despite its name, this rare B-cell lymphoproliferation is considered likely to be unrelated to HCL and, as such, is now categorised separately in the 2008 WHO classification. However it is discussed here because it is important in the differential diagnosis of HCL. In particular it responds differently to standard HCL treatment, being generally resistant to interferon alpha and rarely achieving CR with either pentostatin or cladribine. This disease is described in a chapter separate from that covering HCL ('Splenic B-cell lymphoma/leukaemia unclassifiable') of the WHO classification of haematopoietic tumours, together with splenic diffuse red pulp variant of B-cell lymphoma (Piris *et al*, 2008).

HCL-variant differs from HCL in the lack of monocytopenia and the elevated WBC, in the region of 40–60 x 10^9/l (Sainati *et al*, 1990). Cells in most cases of HCL-v are villous and large, as in HCL, but have a distinct nucleolus and round nucleus resembling B-cell prolymphocytic leukaemia (B-PLL). In some cases they are more polymorphic. In contrast to B-PLL and splenic lymphoma with villous lymphocytes (SLVL), bone marrow and spleen histology is reportedly similar to that seen in HCL (Foucar *et al*, 2008) although published examples of well characterised cases are rare. Bone marrow is often easy to aspirate in HCL-v because the reticulin fibre content is low. The immunophenotype of HCL-v cells (Sainati *et al*, 1990) differs from that of HCL in that CD25 and HC2 are, as a rule, not expressed. CD103 is expressed infrequently and CD11c is nearly always positive. Using the CLL score (Moreau *et al*, 1997) HCL-v will score 0–1, as will HCL, B-PLL and SLVL.

There is no adequate treatment for this condition. In the largest published series (n=58), splenectomy resulted in good partial remission in 2/3 patients (Matutes *et*

al, 2001). Very rarely, patients may achieve CR after 3 or 4 courses of cladribine. There have been 2 case reports documenting haematological CR after treatment with rituximab (Narat *et al*, 2005; Quach *et al,* 2005). In the setting of non-response to nucleoside analogues, rituximab would be a reasonable therapeutic option.

Recommendations

- **It is not possible to make firm recommendations regarding the treatment of HCL-v; additional studies are required.**
- **Splenectomy results in partial remission for some patients. (Grade 2C)**
- **Purine analogues +/- rituximab may benefit some patients. (Grade 2C**)

5. References

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APPENDIX 1

STRENGTH OF RECOMMENDATIONS:

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as ‘suggest’.

QUALITY OF EVIDENCE:

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Table 1 Clinical and laboratory features of HCL (prevalence)

Splenomegaly	**60–70%**
Hepatomegaly	**40–50%**
Abdominal lymph node enlargement*	**10%**
Anaemia: Hb < 100 g/l	**70%**
Thrombocytopenia	**80%**
WBC: < 5 x 10^9/l	**65%**
Neutropenia: < 1 x 10^9/l	**75%**
Monocytopenia: < 0.1 x 10^9/l	**90%**
Hairy cells in PB films	**95%**

***By CT scan investigation**

Table 2 Diagnostic tests for HCL

- **Peripheral blood film**

- **Bone marrow trephine biopsy with H&E and reticulin stains plus immunohistochemistry: CD20, DBA.44, TRAP and additional panel to exclude other small B-cell lymphoproliferations.**
- **Flow cytometry on PB or BM cell suspensions with a panel of McAbs:**
    - **B-cell panel: CD19, CD20, CD22, SmIg**
    - **HCL panel: CD11c, CD25, CD103, CD123**

Table 3 Treatment regimens for HCL

• **Pentostatin** (2′–deoxycoformycin; 2′–DCF)

4 mg/m^2 every 2 weeks until maximum response plus 1 or 2 extra injections. Measure creatinine clearance before treatment – avoid if clearance < 60 ml/min; halve dose if 40–60 ml/min. Give 1.5 l i.v. fluid with each dose of drug. *

IB

• **Cladribine** (2-chlorodeoxyadenosine; 2-CDA) **IB**

0.1 mg/kg/day as a continuous i.v. infusion for 7 days and repeat at 6 months if no CR achieved. *

0.14 mg/kg/day as an i.v. infusion over 2 hours for 5 consecutive days and repeat at 6 months if no CR achieved. *

0.14 mg/kg/day as an i.v. infusion once weekly for 6 consecutive weeks and repeat at 6 months if no CR achieved *

0.14 mg/kg/day as a sc bolus injection for 5 consecutive days and repeat at 6 months if no CR achieved.*

0.14 mg/kg/day as a sc bolus injection once weekly for 5 consecutive weeks and repeat at 6 months if no CR achieved *

- **Rituximab** (6-8 doses in total)

375 mg/m^2 as an i.v. infusion, weekly or fortnightly, delivered either concurrently or sequentially with either purine analogue, in patients failing to achieve CR with either pentostatin or cladribine alone.

IIC

• **Interferon alpha** (IFN-α)
3 mega-units daily until maximum response and continue indefinitely at the same dose 3 times a week.
For very cytopenic patients start at 3 times a week **IIC**

• **Splenectomy**
Indicated if the spleen is very large (e.g. > 10 cm below costal margin) and the BM only moderately involved

IIC

***Blood products should be irradiated**

Table 4 The management of HCL

1.	**Diagnosis**: Bone marrow biopsy and abdominal CT essential
2.	**Choice of therapy** a. Most patients: Cladribine or Pentostatin (see Table 3 for regimens). Aim for CR. b. Patients with large spleens and moderate or little BM involvement may have splenectomy first and nucleoside analogue therapy if/when evidence of progression
3.	**Choice of therapy at relapse** Either pentostatin or cladribine in combination with rituximab
4.	**Monitor response** by BM trephine biopsy with immunocytochemistry (CD20, DBA.44) and abdominal CT (if previously abnormal)
5.	**Prophylaxis** during lymphopenia: co-trimoxazole 960 mg three times per week; aciclovir (200 mg three times daily) may be indicated especially if there is a history of herpetic infection