British Society for Haematology

British Committee for Standards in Haematology

Guidelines on diagnosis and therapy

Hairy cell leukaemia

guidelines

guidelines

Level of evidence

Level	*Type of evidence*
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Grade of recommendation

Grade	*Evidence level*	*Recommendation*
A	Ia, Ib	Required – at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required – availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C	IV	Required – evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities
		Indicates absence of directly applicable clinical studies of good quality

Derived from US Agency for Health Care Policy and Research

Published for and on behalf of the BCSH by

DARWIN
MEDICAL COMMUNICATIONS LTD

13 Napier Court, Abingdon Science Park, Abingdon, Oxfordshire, OX14 3YT, UK

Hairy cell leukaemia

A guideline compiled on behalf of the Clinical Task Force of the British Committee for Standards in Haematology by

Professor Daniel Catovsky

Methods

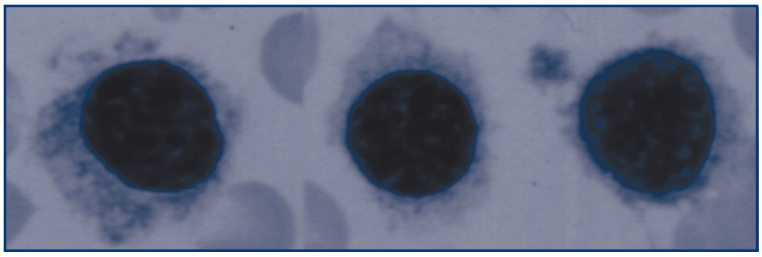
- Provided as a solicited draft guideline
- Reviewed by members of the Clinical Task Force
- Presented at Open Forum to attendees at the BSH Annual Meeting, Brighton, April 1999
- Revised as necessary
- Issued February 2000; due for revision by end of 2002

Clinical Task Force of BCSH: Prof AK Burnett (Chair), Drs D Milligan, R Marcus, J Apperley, P Ganly, S Johnson, J Davies (Secretary), SE Kinsey

Hairy cell leukaemia

1 Introduction

HCL is an uncommon B-cell lymphoproliferative disorder affecting adults, first reported as a distinct disease in 1958[1]. The incidence has been estimated as 2% of all forms of leukaemia and 8% considering only leukaemias of mature B and T cells, including also low/intermediate-grade non-Hodgkin's lymphomas with lymphocytosis > 5 x 10^9/l. HCL is 6–10 times less frequent than chronic lymphocytic leukaemia. A great interest in this disease has evolved in parallel with the development of useful therapeutic agents: alpha-interferon and pentostatin in the 1980s and cladribine in the 1990s. HCL affects middle-aged men more commonly than women; the male:female ratio is 4.5:1.



Hairy cells

Hairy cell leukaemia

2 Clinical and laboratory features

Main laboratory findings are cytopenias, usually affecting two or three lineages; monocytopenia is a consistent feature. Leucocyte counts tend to be low (usually less than 5 x 10^9/l and very rarely over 10 x 10^9/l), except in HCL-variant (see below). Hairy cells are often seen in peripheral blood films but their proportion is variable. A CT scan investigation is necessary to identify patients with abdominal nodes[2]. Splenomegaly was more frequently reported in early series[3] but since the disease is now better recognised, the incidence of splenomegaly has decreased (Table 1).

Table 1 Clinical and laboratory features of HCL (incidence)

Splenomegaly	(60–70%)
Hepatomegaly	(40–50%)
Abdominal nodes*	(15–20%)
Anaemia: Hb < 10 g/dl	(70%)
Thombocytopenia	(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 (5–65%)	(95%)

*By CT scan investigation

3 Diagnostic tests

Careful examination of peripheral blood films will show the characteristic hairy cells, which are twice as large as normal lymphocytes and have a round, oval or kidney-shaped nucleus and a loose chromatin pattern[4]. A definitive diagnosis always requires a bone marrow trephine biopsy, preferably of 2–3 cm in length as the HCL infiltration may be patchy and can be missed in small biopsies. The trephine biopsy shows a unique pattern of infiltration, interstitial or focal, with clear zones in between the cells. Confirmation of the nature of the infiltration is obtained by immunocytochemistry on paraffin sections using CD20 and/or DBA44 and an antibody to tartrate resistant acid phosphatase (TRAP). Reticulin is, as a rule, increased and this explains the difficulty in obtaining a good aspirate and the frequent dry taps. The presence of erythroid precursors allows a successful aspirate in 10% of patients. The films so obtained may also demonstrate the presence of hairy cells.

Additional tests to confirm a diagnosis are recommended when the diagnosis is not clear, particularly when the number of hairy cells in blood films is low, the bone marrow aspirate is a ‘dry tap’ and the core biopsy shows areas of hypocellularity, and even when cells with villous projections are seen but their nature is uncertain.

TRAP has been shown to be a useful cytochemical test for HCL, but currently the trend is to use immunophenotyping with monoclonal antibodies by flow cytometry. The availability of a monoclonal antibody to TRAP which can be used in bone marrow sections, the main diagnostic material for HCL, has obviated the need for the cytochemical test.

Markers of B cells, such as CD19, CD20 and CD22 are always positive. With a battery of five McAbs which define the CLL score[5] HCL gives low scores (0–1), in common with most other B-cell leukaemias, whilst CLL scores 4–5. Hairy cells are CD5 and CD23 negative, express strong SmIg with either K or L chains, and are FMC7 positive. A panel of four antibodies which are specific for hairy cells should be applied whenever this diagnosis is entertained. The HCL panel consists of CD11c, CD25, CD103 and HC2[6]. When 3 or 4 of these reagents are positive they allow the distinction between HCL (scores 3–4) and all other B-cell disorders (scores 0–1). Good quality trephine biopsies are required not only for diagnosis but for monitoring response to treatment. Haematoxy-eosin stains for detecting residual disease in HCL are notoriously difficult to interpret unless immunocytochemistry with at least one of the antibodies CD20, DBA44 or TRAP is used. Of these antibodies, CD20, although not HCL specific, gives the best results. Clusters of positively stained cells are taken as evidence of residual disease.

Hairy cell leukaemia

In exceptional cases, the clue to the diagnosis of HCL can be obtained from the analysis of spleen specimens obtained after splenectomy. The spleen histology shows infiltration of the red pulp with widening of the pulp cords and atrophy of the white pulp. This unique pattern is not seen in any other of the B-cell disorders, in which the white pulp is, as a rule, hypertrophic. Spleen histology could confirm the diagnosis of difficult cases. However, splenectomy is rarely indicated solely for diagnostic purposes (see below).

Table 2 Diagnostic tests for HCL

- Peripheral blood films
- Bone marrow biopsy with special stains on sections: CD20, DBA44, TRAP
- Flow cytometry on PB or BM cell suspensions with a panel of McAbs:
  - B-cell panel: CD19, CD20, CD22, Smlg
  - HCL panel: CD11c, CD25, CD103, HC2

4 Staging and prognostic features

There is no widely agreed system for staging HCL. The disease affects mainly the bone marrow and the spleen and progresses extremely slowly. Most prognostic features relate to the status of both organs. Heavy bone marrow infiltration and a large spleen will result in maximum degrees of cytopenia. Anaemia (< 8 g/dl), neutropenia (< 0.5 x 10^9/l) and thrombocytopenia (< 50 x 10^9/l) in any combination have, in the past, been associated with poor prognosis. However, the early studies were published before the era of effective treatments for this disease, and prognostic factors should possibly now include response to therapy. The response to splenectomy assessed by the improvement of blood counts has been shown to be a reliable prognostic factor and predictor of the need for subsequent therapy, as shown in a single-institution experience[3] and from data from a retrospective multicentre study[7]. Normalisations of blood counts after splenectomy are associated with good prognosis. Evaluation of the bone marrow trephine before splenectomy could also help predict the response to surgery[8]. As splenectomy is not now the main treatment approach in HCL, the above considerations are valid only if splenectomy is considered as part of the overall management (see below).

Patients presenting with bulky abdominal lymphadenopathy respond less well to first-line therapy, as this manifestation may represent a degree of transformation of the disease[2].

Hairy cell leukaemia

5 Treatment

Most patients will require therapy to correct the cytopenias and the associated problems of anaemia, infections and bleeding. Rarely (< 1% of cases) the patient is asymptomatic and the cytopenias are minimal, and it is therefore legitimate to adopt a wait-and-see policy.

The mainstay of the treatment of HCL comprises the two nucleoside analogues pentostatin[9–11] and cladribine[12–14]. Both agents induce a high rate (> 80%) of complete remissions which, in the majority of patients, are prolonged; 15% of patients treated with pentostatin have remained in clinical remission for more than 8 years[15]. There may still be some role for interferon-alpha and splenectomy in the management of HCL. However, neither these nor pentostatin or cladribine have been tested in large randomised trials. Most of the available information derives from published series[9–15]. Because overall survival in HCL is nowadays 95–98% at 5 years, the end points to assess the value of any treatment should be disease-free interval (DFI; remission duration) and event-free survival (EFS). A single-institution sequential study suggests that, as currently used (see Table 3), the DFI after remission is longer with pentostatin than with cladribine, whilst the CR rate is similar with both drugs[15]. The majority of relapsed patients achieve second remission when re-treated with either pentostatin or cladribine. The choice of agent may depend on the duration of the first remission: if short, i.e. < 3 years, use an alternative agent; if long, e.g. > 5 years, use same or other. However, the overall survival, DFI and EFS are better in patients achieving CR than in those only reaching PR[14,15]. There is a small group of patients who have good responses to either agent but tend to relapse at regular intervals (every 2–4 years) and continue to respond to either drug. Evidence in the few non-responders or the rare ones who become refractory suggests a lack of cross-resistance between pentostatin and cladribine. Patients who present with bulky abdominal lymphadenopathy or who develop this at relapse respond less well to either agent[16]. Both pentostatin and cladribine are well tolerated and the only long-term effect (at least 1 year or longer) is lymphopenia.

Table 3 Treatment regimens for HCL

	Level of evidence
• **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 < 50 ml/min; halve dose if 50–60 ml/min. Blood products should be irradiated	IIa, Grade B
• **Cladribine** (2-chlorodeoxyadenosine; 2-CDA) 0.1 mg/kg/day as a continuous i.v. infusion for 7 days and repeat at 6 months if no CR achieved. See page 8 for regimens with shorter-duration infusions. Blood products should be irradiated	IIa, Grade B
• **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	IIa, Grade B
• **Splenectomy** Indicated if the spleen is very large (e.g. > 10 cm bcm) and the BM only moderately involved	IV, Grade C

6 Patient management

Once the diagnosis of HCL is confirmed (see above and Table 2) and intervention indicated, treatment should be initiated with either pentostatin or cladribine (Table 3). Either drug is likely to induce a CR with minimal toxicity. Pentostatin requires a normal creatinine clearance (> 60 ml/min) for the recommended dose but half dose could be given if the clearance is between 40 and 60 ml/min. Anti-sickness medication should be given with each injection and prophylaxis with cotrimoxazole when the patient becomes lymphopenic (< 1 x 10^9/l). Cladribine requires hospitalisation and a continuous infusion for 7 days (see Table 3). It may be possible to give cladribine through an i.v. pump and avoid admission, although this has not been a practice in the UK. Regimens such as once per week for 5–7 weeks, or 5 mg/m^2/day for 5 days as a 1–2 hour infusion, or 0.15 mg/kg by infusions over 2–5 hours have been used elsewhere, with good response rates. However, no comparisons have been made between the week-long and shorter-duration infusions, and therefore there is no information about the durability of responses and EFS with the latter regimens. It is recommended not to give any concomitant drugs during cladribine infusions as patients often develop skin rashes. Cotrimoxazole should be started once treatment is completed, to prevent pneumocystis infections. Patients receiving pentostatin or cladribine should receive irradiated blood components to prevent transfusion-associated graft-versus-host disease[17].

The role of interferon-alpha is nowadays limited to patients who present with severe pancytopenia, particularly low neutrophil and platelet counts. A regimen of 3 mega units 3 times a week will gradually improve blood counts and facilitate the subsequent use of either nucleoside analogue[18,19]. There is also some evidence that improvements in bone marrow function prior to pentostatin may improve long-term results[20] and decrease the number of injections required to achieve remission.

Growth factors, e.g. G-CSF, could 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 indications for splenectomy in HCL have changed since the advent of useful chemotherapy (Table 3). However, it should not be overlooked that a minority of patients (approximately 2% of all cases and 15% of those splenectomised because of a large spleen) may remain in clinical remission with normal counts for periods of 15 to 25 years. 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 as a debulking procedure improves the long-term results. Nevertheless, as with interferon-alpha, it may facilitate the subsequent use of the nucleoside analogues. If a patient is splenectomised, it is important to wait for the full benefits of the splenectomy to be apparent before starting any other therapy. *It is*

therefore recommended to wait for at least 6 months after splenectomy before considering any other therapy. A slow rise in circulating hairy cells is a feature suggestive of subsequent progression. If blood counts normalise and the patient remains asymptomatic, a decision on further treatment could safely be delayed indefinitely. One alternative for patients presenting with severe neutropenia is to prescribe G-CSF shortly before the initiation of chemotherapy and continue until neutrophil counts are safe (e.g. > 1 x 10^9/l). The management of HCL is summarised in Table 4 and Figure 1.

Table 4 The management of HCL

1. **Diagnosis**: Bone marrow biopsy and abdominal CT essential
2. **Choice of therapy**
   a. Most patients: pentostatin (OPD treatment) or cladribine (7 day inpatient or shorter-duration infusions; see Table 3).
   b. Severely cytopenic patients: interferon-alpha for 2–4 months given 3 times a week until blood counts improve, followed by pentostatin or cladribine. G-CSF may correct neutropenia before commencing nucleoside analogue
   c. Patients with large spleens and moderate or little BM involvement may have splenectomy first and either nucleoside analogue if/when evidence of progression
3. **Monitor response** by BM trephine biopsy with immunocytochemistry (CD20, DBA44, TRAP) and abdominal CT (if previously abnormal)
4. **Prophylaxis** during lymphopenia: cotrimoxazole 480 mg/day; acyclovir may be indicated in some patients

Hairy cell leukaemia

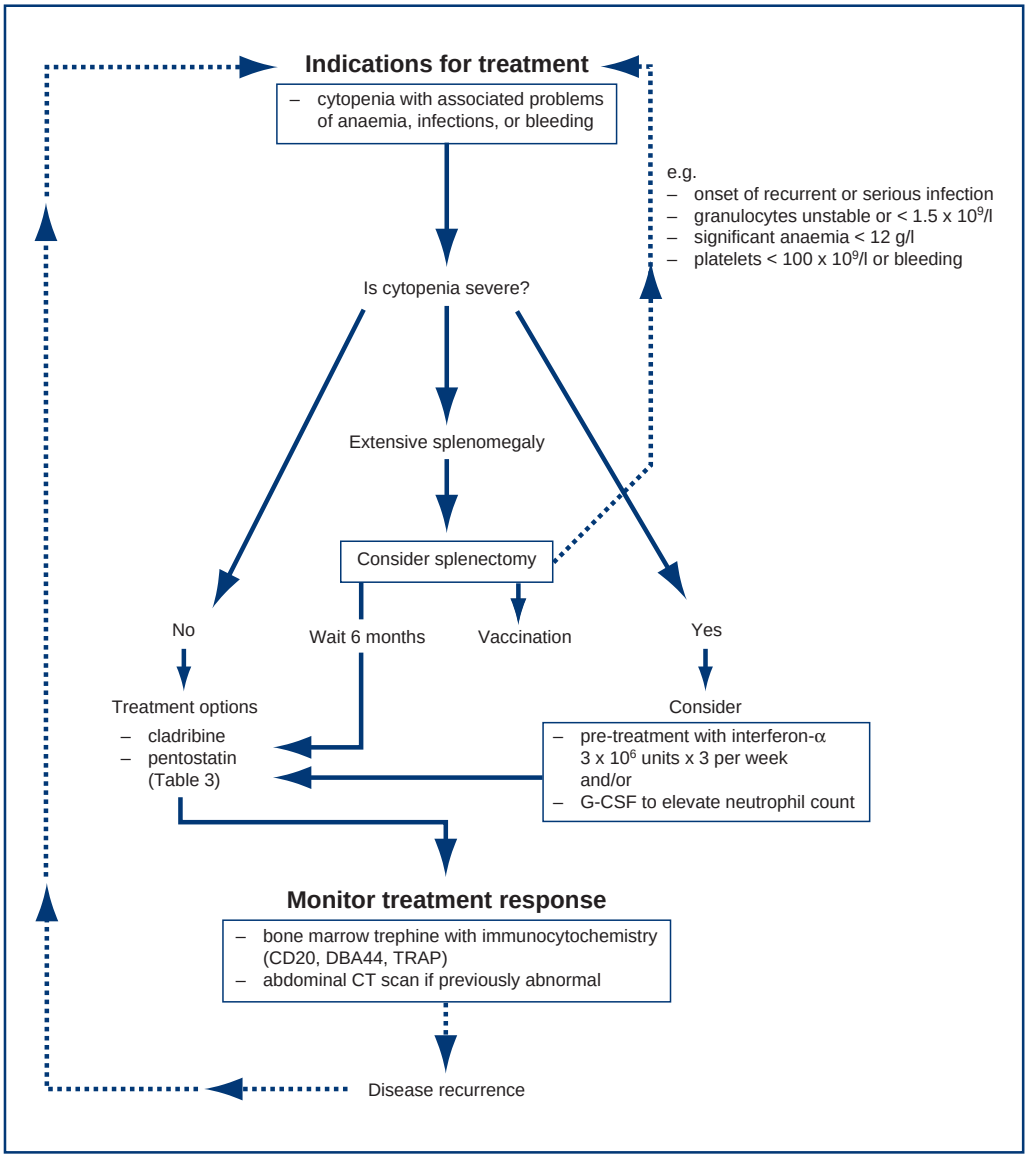


Figure 1 Management of HCL

7 Hairy cell variant

This rare variant of HCL[3,4] is important from the point of view of differential diagnosis and because it is generally resistant to interferon-alpha and rarely achieves CR with either pentostatin or cladribine.

HCL-variant differs from the classic form in the lack of monocytopenia and the elevated WBC, in the region of 40–60 x 10^9/l[19]. HCL-variant cells are villous and large, as in HCL, but have a distinct nucleolus and round nucleus resembling prolymphocytic leukaemia (B-PLL). In contrast with B-PLL and with splenic lymphoma with circulating villous lymphocytes (SLVL), the bone marrow histology (interstitial patterns and spacing around hairy cells) and the spleen histology (predominantly red pulp) are as seen in HCL. The bone marrow is also often easy to aspirate in HCL-variant because the reticular content is low. The immunophenotype of the HCL-variant cells[6,21] differs from that of HCL in that CD25 and HC2 are, as a rule, negative in HCL-variant, CD103 is infrequently expressed, and CD11c is nearly always positive. Thus, the HCL score[6] for most HCL-variant will be 1 or 2 (HCL will score 3 or 4); using the CLL score[5] HCL-variant will score 0–1, the same as HCL, B-PLL and SLVL.

There is no adequate treatment for this condition. Very rarely, patients may achieve CR after 3 or 4 courses of cladribine. There are no reported CRs with any other agent. Splenectomy is often clinically useful in patients with large spleens, but as a palliative procedure. There is little information about other agents, e.g. fludarabine, or combinations, e.g. CHOP.

8 References

1. Bouroncle BA, Wiseman BK, Doan CA. Leukemic reticuloendotheliosis. *Blood* 1958; 13: 609–30.
2. Mercieca J, Puga M, Matutes E, Moskovic E, Salim S, Catovsky D. Incidence and significance of abdominal lymphadenopathy in hairy cell leukemia. *Leuk Lymphoma* 1994; 14(Suppl 1): 79–83.
3. Catovsky D, Foa R. The Lymphoid Leukaemias. Butterworth, London, 1990.
4. Bennett JM, Catovsky D, Daniel M-T *et al.* The French-American-British (FAB) Cooperative Group. Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. *J Clin Pathol* 1989; 42: 567–84.
5. Moreau EJ, Matutes, E, A'Hern RP *et al.* Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal antibody SN8 (CD79b). *Am J Clin Pathol* 1997; 108: 378–82.
6. Matutes E, Morilla R, Owusu-Ankomah K, Houlihan A, Meeus P, Catovsky D. The immunophenotype of hairy cell leukemia (HCL). Proposal for a scoring system to distinguish HCL from B-cell disorders with hairy or villous lymphocytes. *Leuk Lymphoma* 1994; 14(Suppl 1): 57–61.
7. Jansen J, Hermans J. Splenectomy in hairy cell leukemia. A retrospective multicenter analysis. *Cancer* 1981; 47: 2066–76.
8. Golomb HM, Vardiman JW. Response to splenectomy in 65 patients with hairy cell leukemia: an evaluation of spleen weight and bone marrow involvement. *Blood* 1982; 61: 349–52.
9. Catovsky D, Matutes E, Talavera JG *et al.* Long term results with 2'deoxycoformycin in hairy cell leukemia. *Leuk Lymphoma* 1994; 14(Suppl 1): 109–13.
10. Golomb HM, Dodge R, Mick R *et al.* Pentostatin treatment for hairy cell leukemia patients who failed initial therapy with recombinant alpha-interferon: a report of CALGB study 8515. *Leukemia* 1994; 8: 2037–40.
11. Grever M, Kopecky K, Foucar MK *et al.* Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukaemia: An intergoup study. *J Clin Oncol* 1995; 13: 974–82.
12. Hoffman MA, Janson D, Rose E, Rai KR. Treatment of hairy-cell leukemia with cladribine: response, toxicity and long-term follow up. *J Clin Oncol* 1997; 15: 1138–42.
13. Saven A, Burian C, Koziol JA, Piro LD. Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. *Blood* 1998; 92: 1918–26.
14. Lauria F, Rondelli D, Zinzani PL *et al.* Long-lasting complete remission in patients with hairy cell leukemia treated with 2-CdA: a 5-year survey. *Leukemia* 1997; 11: 629–32.
15. Dearden CE, Matutes E, Hilditch BL, Swansbury GJ, Catovsky D. Long-term follow-up of patients with hairy cell leukaemia after treatment with Pentostatin or Cladribine. *Br J Haematol* 1999; 106: 515–19.
16. Mercieca J, Matutes E, Emmett E, Coles H, Catovsky D. 2-chlorodeoxyadenosine in the treatment of hairy cell leukaemia: differences in response in patients with and without abdominal lymphadenopathy. *Br J Haematol* 1996; 93: 409–11.
17. BCSH Blood Transfusion Task Force. Guidelines on gamma irradiation of blood components for the prevention of transfusion-associated graft-versus-host disease. *Transfusion Med* 1996; 6: 261–71.
18. Dearden C, Catovsky D. Treatment of hairy cell leukemia with 2'-deoxycoformycin. *Leuk Lymphoma* 1990; 1: 179–85.
19. Habermann TM, Anderson JW, Cassileth PA, Bennett JM, Oken MM. Sequential administration of recombinant interferon alpha and deoxycoformycin in the treatment of hairy cell leukemia. *Br J Haematol* 1992; 80: 466–71.
20. Catovsky D. Clinical experience with 2'deoxycoformycin. *Hematol Cell Therapy* 1996; 38: S103–S107.
21. Sainati L, Matutes E, Mulligan SP *et al.* A variant form of hairy cell leukemia resistant to alpha-interferon: clinical and phenotypic characteristics of 17 patients. *Blood* 1990; 76: 157–62.

Abbreviations

ALL	acute lymphoblastic leukaemia
ALT	alanine aminotransferase
AML	acute myelogenous leukaemia
BM	bone marrow
CAP	cyclophosphamide + doxorubicin + prednisolone
2-CDA	2-chlorodeoxyadenosine (cladribine)
CHOP	cyclophosphamide + doxorubicin + vincristine + prednisolone
CLL	chronic lymphocytic leukaemia
CML	chronic myelogenous leukaemia
COP	see CVP
CR	complete remission
CT	computerised tomography
CVP	cyclophosphamide + vincristine + prednisolone
2´-DCF	2´-deoxycoformycin (pentostatin)
DFI	disease-free interval
EFS	event-free survival
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte–macrophage colony stimulating factor
Hb	haemoglobin
HC	haemochromatosis
HCL	hairy cell leukaemia
IFN	interferon
LPL	lymphoplasmacytic lymphoma
McAb	monoclonal antibody
MGUS	monoclonal gammopathy of uncertain significance
MRD	median remission duration / minimal residual disease
MS	median survival
NHL	non-Hodgkin’s lymphoma
PB	peripheral blood
PLL	prolymphocytic leukaemia
PR	partial remission
SLVL	splenic lymphoma with villous lymphocytes
SMZL	splenic marginal zone lymphoma
TRAP	tartrate resistant acid phosphatase
UIBC	unsaturated iron-binding capacity
WBC	white blood cell (count)
WM	Waldenström’s macroglobulinaemia

Published for and on behalf of the BCSH by

DARWIN
MEDICAL COMMUNICATIONS LTD

13 Napier Court, Abingdon Science Park, Abingdon, Oxfordshire, OX14 3YT, UK