Chronic Lymphocytic Leukaemia Guidelines

Approved by Pathway Board for Haematological Malignancies

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These guidelines should be read in conjunction with the latest National Cancer Drug Fund information, and all applicable national /international guidance.

Chronic Lymphocytic Leukaemia (CLL)

INTRODUCTION

CLL is the commonest leukaemia in adults with an incidence of 3-4 per 100,000 per year. Median age at presentation is 72 years and it occurs twice as frequently in males as females. However, about 11% of cases occur at ages under 55 years (Howkander *et al*, 2012). There is a familial/genetic predisposition. The natural history of CLL is extremely variable with survival time from initial diagnosis that ranges from 2 to 20 years, and a median survival of approximately 10 years. CLL remains incurable with current chemo-immunotherapy regimens; however, prolonged disease control and minimal residual disease (MRD) negativity can be achieved.

DIAGNOSIS

- In up to 70% of patients the diagnosis of CLL is an incidental finding on FBC
- The diagnosis of CLL is currently based on the combination of lymphocyte morphology, the presence of >5x10^9/l circulating clonal B cells persisting for three months and a characteristic immunophenotype.
- CLL cells typically express weak to weak-moderate monotypic surface immunoglobulin (SIg), CD5, CD19, CD23, CD160 (Farren *et al.* 2011) and weak or absent CD79B, CD22 and FMC7. A recommended panel of monoclonal antibodies and scoring system for the diagnosis of CLL is shown below.

• Marker	• Score 1	• Score 0
• SmIg • CD5 • CD23 • FMC7 • CD22 or CD79B	• Weak-moderate • Positive • Positive • Negative • Weak	• Strong • Negative • Negative • Positive • Strong
• Score > 3 suggestive of CLL; score < 3 suggestive of other B cell malignancy		

- Using this scoring system, 92% of CLL cases score 4 or 5, 6% score 3 and 2% score 1 or 2; all B cell lymphomas score 1 or 2.
- CD5 positivity is present in >90%. If CD5 negative consider alternative diagnoses.
- An alternative “mini score”, incorporating CD5, CD23 and CD160 can also be used (Farren *et al.* 2011).
- Patients with a clonal lymphocyte count between 3 and 5 x 10 9/l, in the absence of lymphadenopathy, splenomegaly or cytopenias, are classified as **clinical monoclonal B- lymphocytosis (MBL)** with a risk of progression to CLL of 1-2% per year.

Differential Diagnosis

- **Small lymphocytic lymphoma (SLL)**

The WHO classification of the malignant lymphoproliferative disorders [4] indicate that CLL and SLL are identical diseases. However, there may be differences in adhesion molecules, which are responsible for differences in tissue distribution. The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Moreover, the number of B lymphocytes in the peripheral blood should not exceed 5×10^9/L. In SLL, the diagnosis should be confirmed by histopathology of a lymph node biopsy.

- **Mantle cell lymphoma**

Morphologically, mantle cell lymphoma (MCL) can be difficult to differentiate from atypical CLL, but classically cells are pleomorphic small lymphocytes with irregular or cleaved nuclei. Like CLL, CD5 expression is characteristic, whereas CD23 is typically negative. The exception is MCL in leukaemic phase, where CD23 expression, albeit at low levels, occurs in upto one third of cases (Farren *et al.* 2011). Unlike B-CLL, cells in MCL stain strongly for cyclin D1 and SIg. The t(11;14) is characteristically identified.

- **Lymphoplasmacytic lymphoma** (Waldenstrom's Macroglobulinaemia)
- **Hairy cell leukaemia**
- **Large granular lymphocyte leukaemia**
- **Mycosis fungoides**
- **Adult T cell lymphoma leukaemia**
- **Prolymphocytic leukaemia**

Prolymphocytes are large cells with somewhat immature-appearing nuclear chromatin, a prominent vesicular nucleolus, and abundant cytoplasm. Other features include massive splenomegaly and hyperlymphocytosis (usually > 100 x 10^9/L).

- Phenotypically, prolymphocytes may be either B-cells or T-cells and are distinct from CLL lymphocytes, having normal amounts of SmIg and negativity for CD5.
- B-PLL is usually CD19, CD20, CD21 and CD24 positive.
- T-PLL variants are CD4+/CD8- (65 %), CD4+/CD8+ (21 %), or CD4-/CD8+ (13 %). The entity formerly called T-CLL is now called T-PLL. Morphologically, T-PLL cells are smaller, have more condensed nuclear chromatin, nuclear irregularity, often inconspicuous nucleoli and cytoplasmic blebbing.

Distinguishing between CLL, MBL and SLL

Criteria	**CLL**	**MBL**	**SLL**
Clonal B cells >5 x 10^9/L	Y	N	N
Disease-related cytopenias	Y/N	N	Y/N
B symptoms	Y/N	N	Y/N
Lymphadenopathy and/or splenomegaly	Y/N	N	Y

EVALUATION AND INVESTIGATIONS AT PRESENTATION
(including asymptomatic Stage A patients at diagnosis)

- History of infections, B symptoms: weight loss, night sweats, fever, extreme lethargy
- Family history of lymphoid malignancy
- ECOG score
- Physical examination for lymphadenopathy/ splenomegaly/ hepatomegaly

Samples sent to SIHMDS for:
- FBC & film
- DAT and reticulocyte count (essential in all anaemic patients and before staring treatment)
- Peripheral blood immunophenotype
- U&E, creatinine, urate, calcium, phosphate
- Liver function tests
- LDH
- Immunoglobulin levels, serum protein electrophoresis
- Beta-2 microglobulin (β2M)

Additional Investigations to consider
- FISH cytogenetic analysis - peripheral blood (in heparin or cytogenetic medium) is the preferred material.
- Peripheral blood for IgHV mutation analysis
- Bone marrow (BM) aspirate & trephine. In the era of FISH analysis, routine BM cytogenetics is not recommended. **Bone marrow is not essential at diagnosis but should be performed prior to therapy and to define complete response after treatment. It is also indicated in determining the cause of cytopenias pre-treatment and prolonged cytopenias post treatment (BCSH 2012).**

- Lymph node biopsy - if the diagnosis is uncertain or to exclude transformation (eg, if there is unusually bulky lymphadenopathy)
- CT scan of neck, chest, abdomen and pelvis. This is generally not essential at diagnosis, but is required pre-treatment to allow post therapy assessment. There is no role for routine surveillance CT scans in asymptomatic patients post treatment.
- If under consideration for alemtuzumab therapy, baseline CMV serostatus
- HLA typing (for patients where an allogeneic transplant maybe an option)

Prior to treatment

- Hepatitis B (including $HepB_s$ Ag, $HepB_s$Ab, $HepB_c$ Ab)
- Hepatitis C Ab
- HIV serostatus
- FISH cytogenetic analysis, specifically, screening for *ATM* and *TP53* deletion and/or mutation should be performed prior to treatment (and repeated at re-treatment)

CLINICAL STAGING

Staging is based on clinical parameters and not on specialist investigations. Two staging systems are used; Binet and Rai.

Modified Rai Clinical Staging System For CLL			
Risk	**Stage**	**Description**	**Median survival**
Low	0	Lymphocytosis in blood or bone marrow	150 months
Intermediate	I	Lymphocytosis + enlarged lymph nodes	101 months
	II	Lymphocytosis + enlarged liver or spleen with or without lymphadenopathy	71 months
High	III	Lymphocytosis + anaemia (Hb <11g/dl) with or without enlarged liver, spleen, or lymph nodes	9 months
	IV	Lymphocytosis + thrombocytopenia (platelet count 100 x 10^9/l) with or without anaemia or enlarged liver, spleen, or lymph nodes	
The Rai System has been modified to consist of three groups • Low risk – Rai stage 0 • Intermediate risk – Rai stages I and II combined • High risk – Rai stages III and IV combined			

Binet Staging System For CLL	
A	Two or less lymphoid areas enlarged*
B	Three or more lymphoid areas enlarged
C	Presence of anaemia (Hb <10g/dl) or thrombocytopenia (platelet count <100 x 10^9/l)
* Five lymphoid bearing areas are possible: cervical, axillary, inguino-femoral, spleen, and liver (whether unilateral or bilateral, each area is counted as one).	
Stage A Progressive is characterised by at least one of the following: • A persistent rise in the lymphocyte count with doubling time <12 months • A downward trend in the Hb and/or platelets • 50% increase in the size of the liver and/or spleen and/or nodes. Appearance of lymphadenopathy, hepatomegaly or splenomegaly if not previously present. • B symptoms: pyrexia, night sweats, weight loss, extreme lethargy	

Binet stage A patients who have Hb >10g/dl, Lymphocytes < $30x10^9$/l, minimal or no lymphadenopathy, non-diffuse pattern of BM involvement and a lymphocyte doubling time of > 12 months have a 80% chance of being alive at 10 years and only 15% are likely to require treatment.

PROGNOSTIC FEATURES

Factors affecting prognosis

Patient related:	Age
	Gender
	Performance status
	Co-morbidities
Disease related:	Disease stage
	Marrow failure
	Immunodeficiency/autoimmunity
	Lymphomatous transformation
	Biomarkers e.g. LDH IgHV mutation status, B2M
Treatment related:	Type of treatment
	Response/toxicity
	MRD status.

Recognised poor prognostic factors include:

- Advanced stage
- Male gender
- Peripheral blood lymphocyte doubling time <12 months (Doubling time for lymphocytes = (initial lymphocyte count)x(no. of months between counts)/ (difference between second and initial lymphocyte count)
- Serum markers. LDH, CD23, thymidine kinase, and β_2-microglobulin may predict survival or progression-free survival
- ZAP70 expression by CLL cells
- CD38 expression by CLL cells
- Mutational status of IgHV. The outcome of patients with CLL cells that use an unmutated IgHV gene is inferior to those patients with a mutated IgHV gene (Damle et al 1999; Hamblin et al 1999). In addition, the HV3-21 gene usage is an unfavorable prognostic marker independent of mutational status (Tobin et al 2002).
- Response to treatment. MRD can be assessed using PCR or multi-parameter flow cytometry. Patients who achieve MRD-negative status appear to have a better prognosis than those without and failure to achieve MRD-negativity predicts for relapse (Moreton et al 2005).

- Cytogenetic abnormalities

Up to 80% of patients have evidence of cytogenetic abnormality using interphase FISH and must be performed before starting treatment. Additional genetic defects may be acquired during the course of the disease, therefore, FISH analysis should be repeated before each line of treatment.

Abnormality	Incidence	Comments
13q-	14-40%	Good prognosis, median survival 133 months
11q- (ATM)	10-32%	Male gender, younger age, bulky LNs Median survival 79 mo with conventional chemotherapy, but may FCR appears to overcome this poor prognosis (Hallek et al 2010)
Trisomy 12	20%	May be associated with a poorer prognosis
17p- (P53) (*TP53* loss or mutation)	5-10% pre 1st Rx 30% in Fludarabine – refractory patients	Poor response to conventional chemotherapy, median survival 32 months.
6q-	2-9%	Plasmacytoid features common, intermediate prognosis

NB A small subset of Stage A patients with *TP53* abnormalities will have stable disease (Best *et al*, 2009; Tam *et al*, 2009).

Although there is no current evidence that prognostic data should influence the timing of initial therapy in individual patients, it does offer insight into the likely natural history of the disease, which many patients value.

- **BCSH Guidelines 2012:**

Measurement of prognostic biomarkers is not currently recommended for patients with early CLL in whom there is no clinical indication for treatment.

Identifying a *TP53* abnormality in patients with no clinical indication for therapy is not an indication for treatment (GRADE B1).

6. Patient information and support, role of CNS and AHP

If the diagnosis of CLL is certain, patients should be informed that CLL is a cancer of the Blood, Bone Marrow and Immune System. Most patients will not require treatment at the time of diagnosis. Their prognosis, which is very variable, should be discussed along with possible treatment options and clinical trials or research studies currently available, as appropriate.

All patients must have access to a Key Worker - this is usually (but not always) the Clinical Nurse Specialist (CNS). Haemato-oncology nurse specialists are trained cancer nurses and their role is to offer emotional support, information and practical advice from the time of diagnosis throughout the course of treatment and aftercare.

The nurse specialist/key worker should be present at diagnosis and at any significant discussion where treatment changes and outcomes are discussed. In the absence of the nurse specialist, a senior nurse may deputise. Where it is not possible for the nurse specialist or a deputy to be present, patients should be given the nurse specialist's contact numbers. The clinician leading the consultation should advice the nurse specialist who should then arrange to make contact with the patient.

As well as dealing with the patient and their reaction to their illness, breaking news to family members especially children and friends can be very difficult and the Haemato-oncology nurse specialist can be invaluable with help and support in what to say and when.

Haemato-Oncology nurse specialists should be available to the patient by telephone or face to face contact to give extra time and support. The nurse must ensure that all patients have a point of contact (both in and out of hours) to discuss any concerns. All patients should be given a card documenting the keyworker/specialist nurse's name and contact number together with an out of hours contact.

The haemato-oncology nurse specialists should continue to be available to patients while they are being followed up or after they are discharged from hospital.

The clinical nurse specialist should ensure that all patients are offered an holistic needs assessment (HNA) at key pathway points including within 31 days of diagnosis, end of each treatment regimen and whenever a person requests one. Following HNA, every patient should be offered a written care plan associated with every HNA completed; this plan should be developed with the patient and communicated to all appropriate health care and allied health care professionals.

Any patient experiencing or reporting reduced mobility and/or ability to perform activities of daily living, should be referred for occupational therapy and physiotherapy assessment.

Written and verbal information is essential and the nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information regarding their condition.

Particularly important aspects of communication and patient information in CLL include the need to address the typically incurable nature of this disease and that it may be managed through the expectant "watch and wait" approach and never require treatment or, alternatively, may require several treatment courses.

The inability to definitively predict when or even if treatment may be appropriate can be a particularly difficult concept for patients to understand and accept. This should be acknowledged, accommodated and addressed as appropriate in each patient's individual management approach

Written and verbal information is essential and the Key Worker / CNS plays a key role in ensuring that patients have access to appropriate and relevant written information regarding their condition . The CNS/Key Worker supports the patient from diagnosis, throughout the treatment pathway, inclusive of end-of-treatment, late-effects and end-of-life care. The CNS/Key Worker acts as patient advocate and is present in the MDT Meetings and ward rounds in order to fulfil this role.

The **Leukaemia & Lymphoma Research Fund** (LLR), **Leukaemia Care** or **Macmillan** information booklets and the NHS Information Prescription are good sources of patient information at diagnosis:
http://www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx
http://www.nhs.uk

The **CLLSA (CLL Support Association)** is another good source of information. This charity is run by patients with CLL to provide support for patients with CLL.
http://www.cllsupport.org.uk

UKCLL Forum is a patient support association http://www.ukcllforum.org.uk/

Lymphoma Association, http://www.lymphomas.org.uk/

Fertility
Consideration of fertility preservation should be made for those of reproductive age

TREATMENT RECOMMENDATIONS

First Line Treatment

Principles

The first decision to be made in CLL is whether the patient requires therapy at the time of initial diagnosis. The disease shows extreme heterogeneity in its presentation and rate of progression, and there is no evidence that early treatment of asymptomatic or stable disease improves long-term survival.

Binet stage A patients generally do not need treatment. Stage A patients who develop AIHA or ITP in the absence of disease progression should be treated in the standard way for the autoimmune phenomenon but do not require cytoreductive therapy. Also, hypogammaglobulinaemia is not an indication for therapy.

Those patients requiring no initial therapy should be monitored at appropriate intervals according to wellbeing and the trend in blood counts – so called "**watch and wait**". Patients with early CLL should be reviewed at least twice within the first year from diagnosis to assess the rate of disease progression. For those with stable disease, particularly if they have 'good risk' clinical and/or laboratory features, monitoring can be extended to an annual check. This may be performed in primary care, in hospital clinics or by distance monitoring schemes (such as the remote Patient Monitoring Programme [rPMP] being piloted at Barts Health NHS Trust).

Indications for treatment

- **Progressive Binet stage A and Binet stage B**
- Non autoimmune anaemia and/or thrombocytopenia
- LDT of < 12 months and other indications of progression (new/increasing nodes/organomegaly) or decreasing haemoglobin/platelets
- lymphadenopathy (bulky, >10cm) / splenomegaly
- B symptoms
- AIHA or ITP poorly responsive to standard therapy
- **Binet stage C (or Rai stage IV)** anaemia and/or thrombocytopenia secondary to marrow infiltration is an indication for treatment

Pre-treatment considerations

- Patient factors: Age, PS, co-morbidities, renal function
- Disease related factors: severity of symptoms, speed of progression, prognostic factors (esp. *TP53* abnormalities)
- Treatment related factors: degree and duration of response to prior therapy, contraindications and side-effects
- Patients receiving **purine-analogues, bendamustine or alemtuzumab** should have **irradiated blood products**. This should be registered in local trust blood bank and the patient given appropriate information and an alert card in case they should be admitted to another hospital

First line therapy regimens

- **Eligible patients should be entered into clinical trials**
- **FCR** (approved by NICE July 2009, TA 174) for fitter (GO-GO) patients with no abnormality of TP53 (caution in patients with renal impairment)
- **Chlorambucil with anti-CD20 antibody (eg Rituximab, Ofatumumab or Obinutuzumab)** for less fit (SLOW-GO) patients with no abnormality of *TP53*. Given imminent NICE approval, both **Ofatumumab** and **Obinutuzumab** may be preferable to **Rituximab**
- **Bendamustine + Rituximab** for intermediate patients (not fit for FCR). Renal impairment is not an absolute contraindication to **Bendamustine**.
- **Alemtuzumab +/- high dose steroids** for patients with abnormalities of *TP53*
- **All patients should be considered for available front-line studies eg FLAIR and RiALTO**
- **Access to agents on CDF should be reviewed (Ibrutinib or Idelalisib+Rituximab)**

Elimination of MRD/Maintenance/Consolidation

- Outside of clinical trials, there is no indication to routinely attempt MRD eradication. **All patients should be considered for available studies studies eg GALACTIC.**
- Outside of clinical trials, there is no indication for ongoing **maintenance** therapy following first line treatment
- As CLL remains incurable with current chemo-immunotherapy, consolidation with an

allogeneic transplant should be considered in *all* fit younger patients (<65 years) with *TP53* deletion/mutation and refractory to fludarabine (no response or relapse within 6 months or those who relapse within 24 months of fludarabine.

Parameter	**CR***	**PR**	**PD**
Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood Lymphocytes	> 4000/µl	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules	50% reduction in marrow infiltrate or B-lymphoid nodules	
Platelet count	> 100.000/µl	> 100.000/µl or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Haemoglobin	> 11.0 g/dl	> 11 g/dl or increase ≥ 50% over baseline	Decrease of > 2 g/dl from baseline secondary to CLL
Neutrophils	>1500/µl	>1500/µl or >50% improvement over baseline	

Response assessment

*CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; CRi is a category defined by failure to recover satisfactory counts but other criteria for CR are met; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of PD and failure to achieve a PR

Second line and subsequent therapy

- Treatment choices following initial treatment depend on response to first line therapy and tolerability. If the response-duration to first line therapy was greater than one year, then 1st line treatment can be repeated
- **Eligible patients should be entered into clinical trials**
- **FCR** may be considered for relapsed/refractory patients **except** when relapse occurs within 24 months following a previous-fludarabine regimen or if refractory to **Fludarabine** (relapsed < 6 months of treatment) or if previously treated with

Rituximab (NICE approved July 2010)

- **Bendamustine + Rituximab** is approved for relapsed therapy

- Those who fail to respond to **Fludarabine**-containing first line therapy or who have a *TP53* del/mutation should receive **Alemtuzumab** therapy with or without **high dose methyl prednisolone**

- **HDMP**+/- **Rituximab**, **dexamethasone+Rituximab**, **Rituximab** alone, **splenectomy** and **radiotherapy** may all be considered as palliative therapy for late-stage refractory patients

- New generation therapies (small molecule BCR and other inhibitors, new anti-CD20 antibodies) have shown excellent results in clinical trials and are likely to become available in the UK in the next 1-2 years. **Idelalisib** is licensed and currently available through the CDF. **Ibrutinib** is also licensed and currently available through the CDF. Both are expected to be evaluated by NICE in 2015

- All patients should be considered for appropriate relapsed/refractory and high risk (*TP53* abnormalities) clinical trials

7. Allogeneic SCT

- European Group for Blood and Marrow Transplantation (EBMT) 2006 recommends that allogeneic transplantation is a reasonable option for fit patients with high risk features:

    - abnormalities of TP53 in first or subsequent remission

    - Non response or early relapse (within 12 months) after purine analogue-containing therapy

    - Relapse within 24 months after purine analogue combination chemo-immunotherapy

- Patients should be referred early to a local transplant centre with appropriate expertise

- Autologous SCT is no longer recommended except in cases of Richters transformation as an alternative to allo-SCT for consolidation after chemotherapy

Richters transformation

- Occurs in about 3-10% CLL patients

- Usually rapid progression in a single nodal site accompanied by a rise in LDH

- May also undergo transformation in BM, CNS or organs (liver, kidneys)

- Treatment Options include**:**
- **Eligible patients should be entered into clinical trials**
    - **CHOP** type regimen + **rituximab**
    - **Platinum** –based regimen +/- **rituximab**
    - Choice is dependent on previous treatment, general fitness of patient etc and should be decided on an individual basis
    - All chemosensitive patients should then be considered for consolidation with autologous or allogeneic HSCT.

B-cell Prolymphocytic Lymphocytic Leukaemia

- Very rare aggressive leukaemia with poor survival
- Morphology and immunophenotype distinct from CLL
- High WBC, massive splenomegaly, minimal lymphadenopathy
- TP53 del/mutation in up to 50%
- Assessment and management as for CLL
- Induction treatment with FCR or BR if no TP53 del, alemtuzumab if TP53 abnormality
- Consolidation with SCT in eligible patients
- Splenectomy may be beneficial in resistant cases
- Supportive care as for CLL

Management of disease related complications

Autoimmune Haemolytic Anaemia or Thrombocytopenia

- Autoimmune haemolytic anaemia is reported in 10-20% of CLL patients,

  and ITP in 2-5%. PRCA and auto-immune neutropenia are rarer but probably under-recognised
- AIHA or ITP should be treated before deciding whether therapy for CLL is needed
- Patients with warm AIHA or ITP should be treated according to guidelines for idiopathic AIHA or ITP:
    - Prednisolone at 1 mg/kg body weight per day for 2-4 weeks, tapering off over several weeks.
    - For ITP, IVIG 1g/kg as a single infusion (responses are transient) or 0.4/kg over 5 days can be used if immediate response is required (eg before surgery).
    - Cyclosporine A or MMF may be indicated in resistant cases or to maintain response and allow withdrawal of steroids
    - Rituximab 375 mg/m2 weekly x 4-6 (some studies have used 100mg rituximab weekly with good effect)

- Combination therapy with rituximab, cyclophosphamide and dexamethasone can be used in resistant cases
- Splenectomy
- Avoid re-treatment with fludarabine in patients with a previous history of purine analogue related AIHA or ITP.
- TPO-R agonists (eltrombopag/romiplostim) can be helpful in resistant ITP.

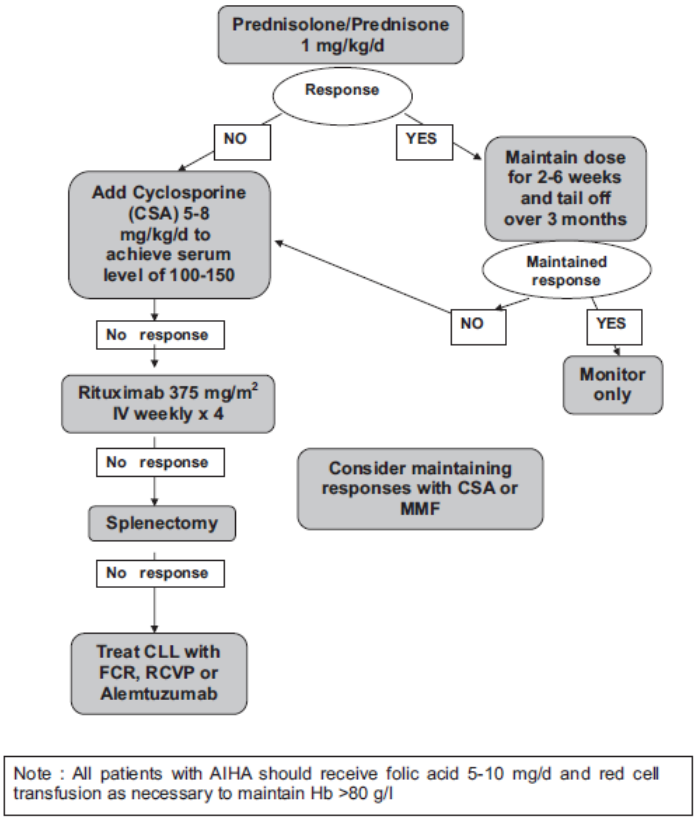

Fig 1. Treatment algorithm for AIHA/ITP. Adapted from Dearden ASH Education Supplement 2008 (Dearden, 2008). With permission from the American Society of Hematology © 2008.

Infection

- Infective complications are a common clinical problem and account for the majority of CLL deaths

- Susceptibility is multifactorial and due to the disease itself and as a result of therapy and includes hypogammaglobulinaemia, neutropenia, impaired T and natural killer cell function and defective complement activity

- Most infections are bacterial but fungal, viral and opportunistic infections are increasingly prevalent with newer treatments (purine analogues, alemtuzumab and methyl prednisolone)

- All patients should receive vaccination against encapsulated bacteria (pneumococcus, HIB) and annual influenza but NOT live vaccinations (including the current shingles vaccine)

Advice on the use of specific vaccines is available at

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917

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- All infections should be treated vigorously, especially in those patients receiving treatment and/or with a prior history, and patients given information to contact their doctor or the CNS at the first sign of infection for advice

- Up to 70% of patients with CLL have hypogammaglobulinaemia and IVIG is recommended for those with recurrent severe infectionsdespite prophylactic antibiotics.

- Patients receiving purine-analogue containing chemotherapy will usually receive PCP and herpes prophylaxis. In addition those patients receiving high dose steroids should also have anti-fungal prophylaxis and those receiving alemtuzumab require weekly monitoring for CMV reactivation

- The use of G-CSF should be considered in patients with prolonged/severe neutropenia post chemotherapy

Supportive care and rehabilitation

REHABILITATION AND SURVIVORSHIP

Issues in relation to rehabilitation, long term consequences of treatment and survivorship should be monitored throughout the patient pathway and highlighted to the appropriate Allied Health Professionals if required. Survivorship issues can relate to the effects of the disease process and / or management of long-term adverse effects of treatment.

Referrals include:

- Physiotherapist/ occupational therapist (fatigue management, rehabilitation, reduced mobility)
- dietitian if symptoms impacting on intake/nutritional status especially in cases of GI disturbances and mucositis, weight loss
- speech and language therapist (weight loss, dysphagia or concerns regarding aspiration)
- information leaflets on neutropenic diets and 'eating well with cancer' should be made available

Any patient experiencing or reporting reduced mobility and/or ability to perform activities of daily living, should be referred for occupational therapy and physiotherapy assessment

If an in-patient:

- Any patient showing signs of respiratory distress should be referred for respiratory physiotherapy assessment in accordance with local on-call guidelines, unless of overt metabolic cause
- A screening tool for assessment of dietary issues should be completed weekly and if issues identified, a referral to specialist dietitian made

Any patient showing signs of non-acute breathlessness should be referred to specialist occupational therapy or physiotherapy for assessment and intervention

Referral for Specialist dietietic input should be made in the following instances:

- Any patient with neutropenia should be provided with information and education on the neutropenic diet and have a referral made to a specialist dietitian
- If artificial feeding is being considered, a referral to the specialist dietitian should be made
- Any patient with mucocitis should be referred for dietetic assessment as well as for specialist speech and language assessment
- Weight loss/malnutrition identified through weekly screening of inpatients

People reporting pain should be considered for non-pharmacological intervention including but not limited to, TNS, complementary therapy and psychological intervention such as mindfulness

End of treatment information

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary. The end of treatment summary should be completed by the named CNS / Key Worker with the patient and a copy sent to the GP and the patient. Patients who remain untreated on watch and wait follow up should aim to have an annual HNA.

People should be offered access to a health and wellbeing clinic at the end of treatment. This should provide information to enable a person to self-manage any expected consequences of their cancer and its treatment, as well as general health promotion information, including diet and physical activity.

The MDT outcome form and clinic letters will serve to communicate diagnosis, treatment initiation and new lines of treatment with the GP.

FOLLOW-UP ARRANGEMENTS

- Stage A patients with stable disease require review every 6-12 months depending on age etc. this can be undertaken by the GP in many cases with agreed triggers for referral back to the haematology team
- Patients with progressive disease will require more frequent monitoring (q 1-3 monthly) depending on pace of change
- Patients on treatment should be seen once every 2-4 weeks
- Patients on F/U after completion of treatment should be seen monthly until recovery is secure and then every 3-6 months depending on clinical circumstances
- Increasingly, distance monitoring schemes (such as the remote Patient Monitoring Programme [rPMP] being piloted at Barts Health NHS Trust) will be able to deliver follow-up care without the patient needing to attend clinics, while maintaining oversight from the tertiary centre

END OF LIFE CARE

Full integration with Palliative care services should be seamless and end of life treatment decisions fully discussed with patients and their families where appropriate, fully respecting the dignity of patients and the sensitivities of traumatic difficult situations.

For older patients and in those with poor performance status and / or high risk disease, discussions regarding prognosis and treatment options should also include discussions on end-of-life care. These are to facilitate transitions between active disease-modifying therapy to clinical trials, or supportive care only at the time of disease progression / non-response. The named Clinical Nurse Specialist / Key Worker, patient, family members and palliative care teams as well as members of the inpatient ward team may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual. Referral to specialist palliative care should be made using the specific referral form

11. Research and clinical trials

Where possible all eligible patients should be entered into an appropriate clinical trial and consideration should be given to referring a patient to a specialist centre where a suitable trial may be open. Biobanking strategies should be developed through the HMDS.

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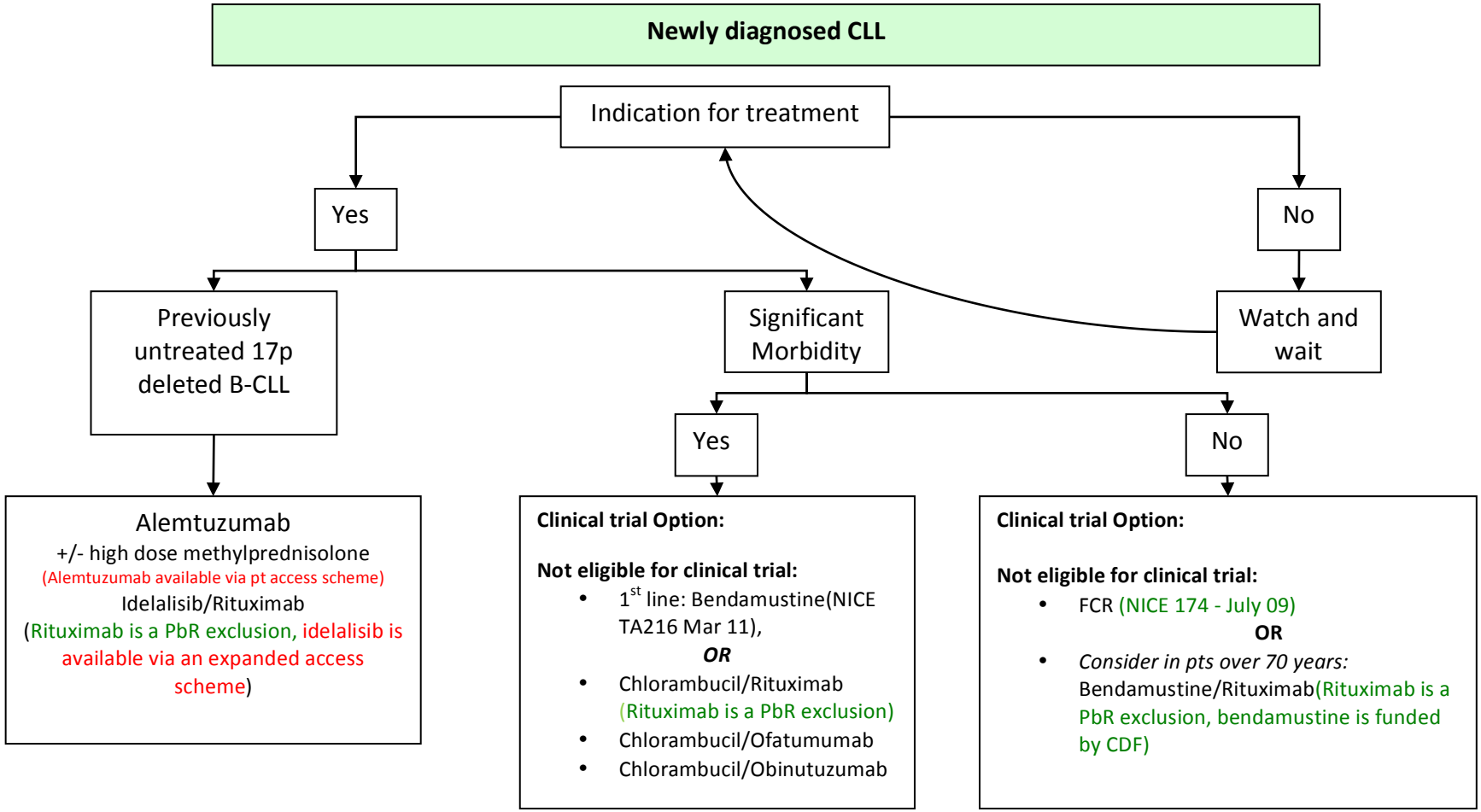
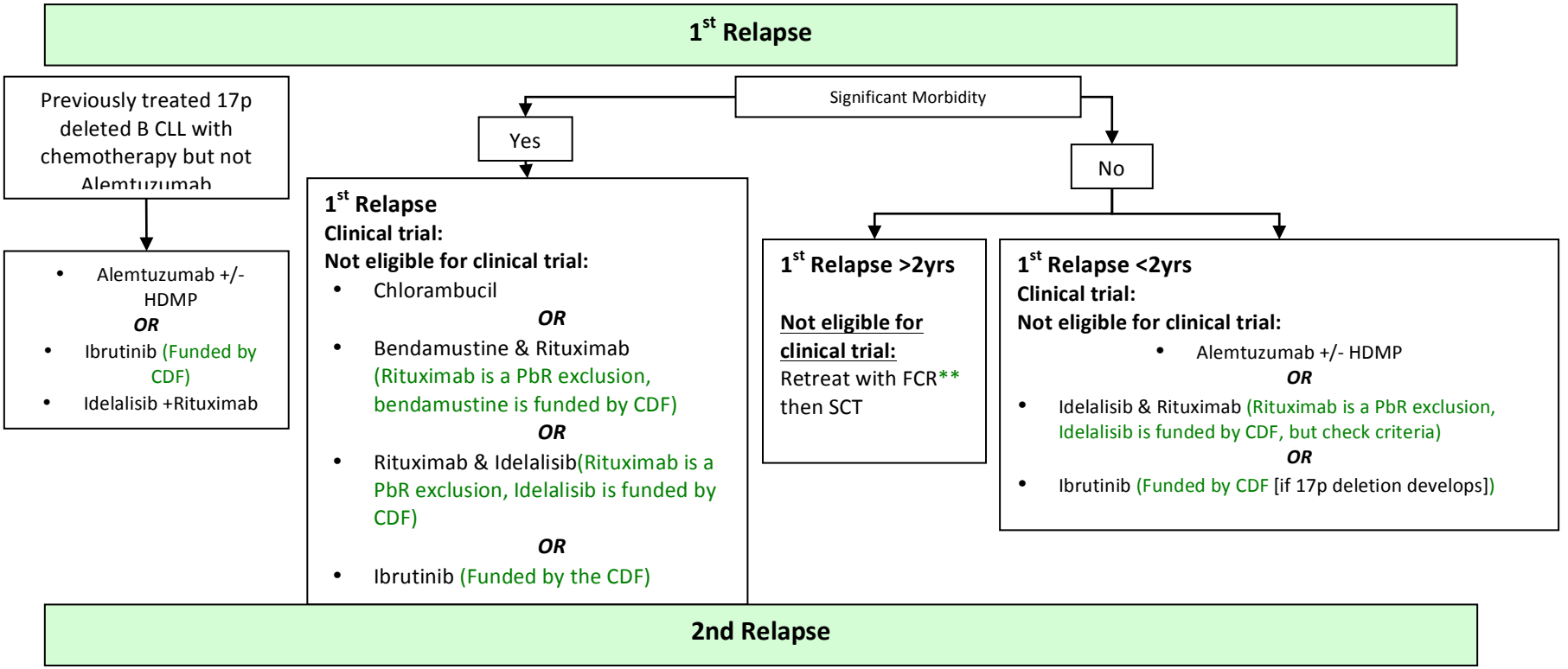
Chronic Lymphocytic Leukaemia Chemotherapy Treatment Outline Algorithms




1st Relapse
Previously treated 17p deleted B CLL with chemotherapy but not Alemtuzumab
• Alemtuzumab +/- HDMP
OR
• Ibrutinib (Funded by CDF)
• Idelalisib +Rituximab
Significant Morbidity
Yes
No
1st Relapse
Clinical trial:
Not eligible for clinical trial:
• Chlorambucil
OR
• Bendamustine & Rituximab (Rituximab is a PbR exclusion, bendamustine is funded by CDF)
OR
• Rituximab & Idelalisib(Rituximab is a PbR exclusion, Idelalisib is funded by CDF)
OR
• Ibrutinib (Funded by the CDF)
1st Relapse >2yrs
Not eligible for clinical trial:
Retreat with FCR** then SCT
1st Relapse <2yrs
Clinical trial:
Not eligible for clinical trial:
• Alemtuzumab +/- HDMP
OR
• Idelalisib & Rituximab (Rituximab is a PbR exclusion, Idelalisib is funded by CDF, but check criteria)
OR
• Ibrutinib (Funded by CDF [if 17p deletion develops])
2nd Relapse
2nd Relapse – active treatment
Clinical trial:
Not eligible for clinical trial:
• Alemtuzumab (Alemtuzumab available via pt access scheme)+/- HDMP
OR
• Rituximab & Idelalisib(Rituximab is a PbR exclusion, Idelalisib is funded by CDF)
OR
• Ibrutinib (Funded by CDF)
2nd Relapse or greater - palliation
Clinical trial:
Not eligible for clinical trial:
• Dexamethasone + Rituximab
OR
• HDMP +/- Rituximab
OR
• Rituximab alone; splenectomy; radiotherapy

FUNDING EXPLANATION

* has not been presented/approved at Cancer D&T committee therefore each application will requires chairman's action & ICDFR application for funding

**

1. If patient had FCR 1st line as per **NICE TA174** then retreating with FCR 2nd line is outside **NICE TA193 (July 2010**). Patient will require PCT application for funding.
2. If patient had previous treatment which includes a lower dose than currently licensed of rituximab and/or with chemotherapy other than FC then subsequent treatment with FCR falls within **NICE TA193**. Patient will not require PCT application for funding.

NICE TA 216 March 2011

Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

Please see up to date CDF forms and CDF funding criteria at www.blueteq.com/cdf