

Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia

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The guideline group was selected to be representative of UK based medical experts and patients representatives. Recommendations are based on a review of the literature using Medline/Pubmed searches under the heading, chronic lymphocytic leukaemia, up to August 2011, and data presented at the American Society of Haematology in 2011. The writing group produced the draft guideline, which was subsequently revised by 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 British Committee for Standards in Haematology (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 are available in the BCSH guideline pack http://www.bcsghguidelines.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html. The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia. In all cases individual patient circumstances may dictate an alternative approach.

Epidemiology

The age-adjusted incidence rate of CLL in the UK and USA is 4.2 per 100 000 per year. The incidence increases with age, is higher in men than women and higher in Caucasians than in other racial groups. The median age at presentation is 72 years and 11% of patients are diagnosed under the age of 55 years (Howlader *et al*, 2012).

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Epidemiological surveys have shown a sevenfold increase in CLL and a 2.5-fold increase in other lymphoid malignancies, especially lymphoplasmacytoid lymphoma and hairy cell leukaemia, in the relatives of patients with CLL (Goldin *et al*, 2009). Genome-wide association studies, genotyping single nucleotide polymorphisms in large numbers of patients with CLL and controls provide evidence for a series of loci associated with slightly increased susceptibility to CLL (Di Bernardo *et al*, 2008; Enjuanes *et al*, 2008; Crowther-Swanepoel *et al*, 2010).

Recommendation

- **In view of the low absolute risk of CLL developing in a family member of a patient with CLL and the absence of clinical benefit associated with early diagnosis, there is no current indication to screen family members for the presence of a circulating clonal B cell population (unless they are potential allogeneic haemopoietic stem cell transplant donors) or for genetic susceptibility (Grade B1).**

Diagnosis

The diagnosis of CLL is currently based on the combination of lymphocyte morphology, the presence of $>5 \times 10^9/l$ circulating clonal B cells persisting for >3 months and a characteristic immunophenotype (Bene *et al*, 2011). A recommended scoring system allocates one point each for the expression of weak surface membrane immunoglobulins, CD5, CD23, and absent or low expression of CD79b and FMC7 (Moreau *et al*, 1997). Using this system, 92% of CLL cases score 4 or 5, 6% score 3 and 2% score 1 or 2.

The differential diagnosis of a CD5-positive chronic lymphoproliferative disorder with a low score includes CLL, especially cases with atypical lymphocyte morphology and/or trisomy 12 (Cro *et al*, 2010), mantle-cell lymphoma and marginal zone lymphomas. Additional investigations, including

cytogenetic analysis and histology, may be required to obtain a definitive diagnosis (Dronca *et al*, 2010).

Three disorders, namely CLL, 'clinical' CD5+ve monoclonal B cell lymphocytosis (cMBL), i.e., those cases of MBL with a lymphocytosis detectable on a routine full blood count, and small lymphocytic lymphoma (SLL) share a common immunophenotype, lymphocyte morphology and/or histology and similar biological features (Marti *et al*, 2005; Hallek *et al*, 2008; Muller-Hermelink *et al*, 2008; Rawstron & Hillmen, 2010; Gibson *et al*, 2011)). Distinguishing features are shown in Table I.

Clinical and laboratory evaluation

Clinical evaluation

Patients may present with lymphadenopathy, systemic symptoms such as tiredness, night sweats and weight loss or the symptoms of anaemia or infection. However, more than 80% of patients are now diagnosed as an incidental finding on a routine full blood count. Clinical evaluation should elicit a family history of lymphoid malignancy, define the clinical stage (Table II) and determine whether B symptoms (fever, weight loss, night sweats), profound lethargy and cytopenias are CLL-related, due to marrow infiltration, immune destruction or hypersplenism, or have an alternative cause.

Table I. Distinguishing between CLL, MBL and SLL.

Criteria	CLL	MBL	SLL
Clonal B lymphocytes $> 5 \times 10^9/l$	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

CLL, chronic lymphocytic leukaemia; MBL, monoclonal B cell lymphocytosis; SLL, small lymphocytic leukaemia; Y, yes; N, no.

Table II. Staging systems in CLL.

BINET Stage		Features
A		< 3 Lymphoid areas*
B		≥ 3 Lymphoid areas
C		Haemoglobin < 100 g/l or platelet count $< 100 \times 10^9/l$
RAI Stage	Risk group	Features
0	Low	Lymphocytosis only
I		Lymphadenopathy
II	Intermediate	Hepatomegaly or splenomegaly + lymphocytosis
III/IV	High	Haemoglobin < 110 g/l or platelet count $< 100 \times 10^9/l$

*The five lymphoid areas comprise: uni or bilateral cervical, axillary and inguinal lymphoid, hepatomegaly and splenomegaly

Investigations

The investigation of asymptomatic stage A patients at diagnosis should include: full blood count, reticulocyte count, direct antiglobulin test (DAT), immunophenotype, routine biochemistry and serum immunoglobulins. Additional tests required pre-treatment, include screening for *TP53* deletion and for hepatitis B and C infection in patients who are to receive intensive chemotherapy and/or immunotherapy. Human immunodeficiency virus (HIV) testing should be performed according to UK national guidelines [British HIV Association (BHIVA), 2008].

Marrow examination is not essential for the diagnosis of CLL, but is mandatory to define complete response. It is also indicated in determining the cause of cytopenias pre treatment and prolonged cytopenias post-treatment.

Lymph node biopsy is indicated when there is diagnostic uncertainty or clinical suspicion of lymphomatous transformation (see below).

While computerized tomography (CT) scanning is mandatory in patients entered into clinical trials, the role of imaging in routine practice remains controversial. CT scanning has the potential to identify small volume nodal and/or splenic enlargement in patients who would otherwise be diagnosed as having cMBL or stage A, Rai 0 disease, to identify bulky disease in previously untreated or relapsed patients with no other indication for therapy, to provide a more accurate assessment of treatment response and to detect incidental abnormalities which might influence clinical management. Very few studies have addressed the clinical benefits of this additional information (Hallek *et al*, 2008; Norin *et al*, 2010; Eichhorst *et al*, 2011). There is no evidence to support the routine use of imaging in asymptomatic stage A CLL or cMBL (Muntanola *et al*, 2007; Scarfo *et al*, 2012). If there is clinical concern regarding the possibility of significant thoracic, abdominal or pelvic nodal disease, or of disease transformation, then a CT scan is indicated using standard indolent lymphoma protocols. Consensus UK expert opinion supports the routine use of pre- and post-treatment CT scans in patients managed with more intensive therapies. There is no evidence to support on-going routine CT surveillance scanning of asymptomatic patients following treatment for CLL.

Recommendations

- Patients should be screened for a *TP53* deletion pre-treatment (Grade A1).
- Patients receiving intensive chemo- or immune-therapy should be screened for hepatitis B and C infection (Grade A1).
- Pre- and post-treatment CT scanning should be considered for patients treated with more intensive therapies. There is no role for routine surveillance CT scans in asymptomatic patients post-treatment (Grade C2).

Diagnosis of lymphomatous transformation

Lymphomas develop in 5–15% of patients with CLL, either pre- or post-therapy. The varying incidence partly reflects the requirement for histological diagnosis and differing policies on the indications for tissue biopsy in CLL (Tsimberidou & Keating, 2005; Rossi *et al*, 2008, 2009). Histological appearances resemble diffuse large B cell lymphoma (DLBCL) in approximately 80% of cases and Hodgkin lymphoma (HL) in the remainder. Clinical features suggestive of lymphomatous transformation include bulky (>5 cm) lymphadenopathy, rapid nodal enlargement, the appearance of extra nodal disease, the development of B symptoms and marked elevation of lactate dehydrogenase (LDH). As lymphomatous transformation may be localized, biopsy should be directed to the most suspicious clinical site. Positron emission tomography (PET)/CT scanning may help in the choice of the lesion to biopsy (Bruzzi *et al*, 2006).

Recommendation

- **The possibility of lymphomatous transformation should be considered in patients with bulky or progressive asymmetric lymphadenopathy, high LDH, extranodal lesions and/or unexplained B symptoms (Grade A1).**

Assessing prognosis

The prognosis of patients with CLL is dependent on a variety of patient, disease and treatment-related factors (Table III). Disease-related factors include biomarkers able to predict prognosis and those able to predict response to specific treatments.

Early CLL. The Binet and Rai staging systems predict outcome in patients presenting with widespread and/or bulky lymphadenopathy, hepatosplenomegaly or marrow failure but are insensitive to the clinical heterogeneity within early CLL, i.e. those cases with a low tumour burden who have Binet stage A or Rai stage 0/1 disease (Rai *et al*, 1975; Binet *et al*, 1977). Adding simple clinical and laboratory parameters, such as age, gender, lymphocyte count, lymphocyte doubling

Table III. Factors affecting the prognosis of patients with CLL.

Patient-related	Age
	Gender
	Performance status
	Co-morbidities
Disease-related	Disease stage
	Marrow failure
	Immunodeficiency/autoimmunity
	Lymphomatous transformation
Treatment-related	Biomarkers
	Type of treatment
	Response/toxicity
	Minimal residual disease status

time (LDT) and serum beta 2 microglobulin (B2M) to clinical stage improves the prediction of overall survival (OS) (Wierda *et al*, 2007; Shanafelt *et al*, 2009a) and time to first treatment in early stage CLL (Molica *et al*, 2010; Bulian *et al*, 2011).

These parameters and an increasing number of biomarkers (reviewed in Dal-Bo *et al*, 2009; Furman, 2010; Stamatopoulos *et al*, 2010) enable patients to be classified as being at low, intermediate or high risk of disease progression. However, the difficulty of extrapolating population data to individual patients is highlighted by recent studies identifying a small subset of stage A patients with *TP53* abnormalities who, nevertheless 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, we recognize that some patients will still wish to have the clearest possible idea of the likely natural history of their disease. If biomarkers are measured, then a minimum set of investigations should include *IGHV* gene analysis, serum B2M (interpreted in relation to renal function) CD38 expression and a screen for genomic abnormalities. The results must be interpreted in the clinical context, especially taking account of the patient's age, significant comorbidities and evidence of disease progression since diagnosis (Shanafelt *et al*, 2010).

Recommendations

- **Measurement of prognostic biomarkers is not currently recommended for patients with early CLL in whom there is no clinical indication for treatment (Grade B2).**
- **Identifying a *TP53* abnormality in patients with no clinical indication for therapy is not an indication for treatment (Grade B1).**

Pre-treatment. *TP53* loss occurs in 5–10% of patients at the time of initial therapy and in 30% of patients with fludarabine-refractory disease. A further 5% of patients prior to initial therapy and 12% with refractory disease, have a *TP53* mutation without loss of the other allele and would not be detected by fluorescence *in situ* hybridization (FISH) (Stilgenbauer *et al*, 2009; Oscier *et al*, 2010; Zenz *et al*, 2010a; Gonzalez *et al*, 2011; Pospisilova *et al*, 2012). Both retrospective and prospective studies of previously untreated patients and those with relapsed CLL show that patients with *TP53* loss and/or mutation, have a significantly lower response rate and short progression-free survival (PFS) and OS, when treated with an alkylating agent, purine analogue, bendamustine, mitoxantrone and rituximab alone or in combination (Table IV). In contrast, *TP53* status has much less effect on the response of patients treated with agents such as alemtuzumab, which kill CLL cells through a *TP53*-independent mechanism.

Unmutated *IGHV* genes, use of the stereotypic *IGHV3-21*, deletion of 11q and a raised B2M, independent of clinical stage, also correlated with reduced PFS and OS in a clinical trial of alkylating agent and purine analogue treatment (Oscier

Table IV. Incidence of *TP53* abnormalities in CLL.

Study	Patients (<i>n</i>)	Patient characteristics	% with <i>TP53</i> mutation	% with <i>TP53</i>		Outcome
				% with 17p loss	mutation without 17p loss	
Zainuddin <i>et al</i> (2011)	268	At diagnosis 77% stage A	3.7	3.7	1.1	Both <i>TP53</i> mutation and del 17p associated with TTFT and OS
Rossi <i>et al</i> (2009)	297	At diagnosis 75% stage A	10.0	12.7	3.0	<i>TP53</i> mutations were an independent predictor of short OS
Zenz <i>et al</i> (2010a) (GCLLSG: CLL4 trial)	328	At trial entry F v FC	8.5	4.8	4.5	<i>TP53</i> mutations were the strongest predictor of short PFS and OS in multivariate analyses
Gonzalez <i>et al</i> (2011) (UK LRF: CLL4 trial)	529	At trial entry Chlor v F v FC	7.6	6.3	3.0	<i>TP53</i> mutations were the strongest predictor of short PFS in multivariate analyses
Zenz <i>et al</i> (2010b) (GCLLSG: CLL8 trial)	767	F-refractory	43.8	34.4	N/A	
		PFS 6–12 months	23.5	28.1	N/A	
		PFS 12–24 months	18.1	11.3	N/A	
		PFS > 24 months	4.1	1.5	N/A	
Zenz <i>et al</i> (2009) (GCLLSG: CLL2H trial)		F-refractory treated with alemtuzumab	37	32.3	12.1	No report of <i>TP53</i> mutation or 17p loss on outcome

GCLLSG, German Chronic Lymphocytic Leukaemia Study Group; UK LRF, United Kingdom Leukaemia Research Fund; Chlor, chlorambucil; F, fludarabine; FC, fludarabine + cyclophosphamide; PFS, progression-free survival; NA; not available; TTFT, time to first treatment; OS, overall survival.

et al, 2010). Data from the CLL8 trial comparing FC v FCR indicates that the adverse prognostic significance of del11q may be largely overcome by the addition of rituximab to FC (Hallek *et al*, 2010). It is currently unclear whether the combination of an anti CD20 antibody with other chemotherapy regimens also improves the outcome of patients with del11q.

Recommendations

- **Patients should be screened for the presence of a *TP53* abnormality prior to initial and subsequent treatment. Currently, *TP53* loss should be assessed by FISH. Patients should also be screened for *TP53* mutations when this assay becomes routinely available (Grade B2).**
- **Measurement of biomarkers other than *TP53* loss is not currently recommended outside clinical trials in patients for whom there is a clinical indication for therapy (Grade C2).**

Management

Indications for treatment

Patients with active disease, as defined in the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidelines (Hallek *et al*, 2008), usually benefit from anti leukaemic therapy (Table V). These criteria apply to both previously untreated and relapsed patients. Neither a high

Table V. Indications for treatment.

Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia
Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
Massive nodes (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of <6 months. In patients with initial blood lymphocyte counts <30 × 10 ⁹ /l, LDT should not be used as a single parameter to define a treatment indication.
Autoimmune anaemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.
Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs
Unintentional weight loss of 10% or more within the previous 6 months;
Significant fatigue (i.e., Eastern Cooperative Oncology Group Performance Score 2 or worse; inability to work or perform usual activities);
Fever higher than 38.0°C for two or more weeks without other evidence of infection; or
Night sweats for more than 1 month without evidence of infection.

lymphocyte count, in the absence of a rapid LDT or clinical features of hyperviscosity, nor hypogammaglobulinaemia in the absence of serious or recurrent infection is an indication

for treatment. The timing of treatment, especially in asymptomatic patients, depends in part upon the rate of disease progression. It is important not to delay treatment to the point at which it may be less effective and/or more difficult to administer (e.g. due to cytopenias) especially in patients with 'high risk' CLL.

Factors influencing the choice and duration of treatment

The clinical heterogeneity of CLL and advanced age of many patients dictate that no single treatment approach is applicable to all patients.

Factors influencing the choice of treatment include an assessment of fitness to tolerate chemotherapy and/or immunotherapy, *TP53* status, previous or current immune cytopenias and evidence of lymphomatous transformation (Goede & Hallek, 2011). In previously treated patients, the number and nature of prior treatments, their efficacy and toxicity and the availability of a transplant donor should all be taken into consideration.

Assessing fitness for treatment. Patients requiring treatment should be assessed for their ability to tolerate myelosuppressive and immunosuppressive therapies. Important factors include age, performance status, significant co-morbid conditions, especially a creatinine clearance of <60 ml/min and susceptibility to infection. The use of scoring systems, such as the Cumulative Illness Rating Scale (CIRS) score may be helpful, but none of the currently used scores is CLL-specific and careful assessment of individual patients remains paramount (Miller *et al*, 1992; Extermann *et al*, 1998). Although the outcome of patients over the age of 65–70 years entered into clinical trials of FC and FCR was comparable to that of younger patients (Catovsky *et al*, 2007; Hallek *et al*, 2010), this data should not be extrapolated to elderly patients with

co-morbidities, as these patients have a higher incidence of myelosuppression, often fail to tolerate a full course of treatment and generally have a poorer outcome with therapy (Tam *et al*, 2008).

Importance of achieving a maximal response. Almost all clinical trials have shown that the better a patient responds to therapy the longer their remission, especially in the absence of detectable minimal residual disease (MRD) (Moreton *et al*, 2005; Bosch *et al*, 2008). Recent data from the German CLL8 trial showed an improvement in the depth of remission between cycles 3 and 6, and that achieving an MRD negative remission is an independent marker for improved OS as well as PFS (Bottcher *et al*, 2012). These data provide a clear rationale for the use of the most effective available initial treatment and for completing six cycles of treatment providing toxicity is acceptable.

Definitions of response, relapse, refractory and high risk disease

IWCLL criteria for complete response (CR), partial response (PR) and progressive disease are shown in Table VI. The IWCLL define relapse as disease progression at least 6 months after achieving a CR or PR. Refractory disease is currently defined as treatment failure or disease progression within 6 months of anti-leukaemic therapy. However, the duration of response that should influence the choice of second line therapy is an area of continuing debate (Zenz *et al*, 2012). Patients entered into the German CLL8 trial who had a PFS of <12, 12–24 or >24 months had an OS from the time of second line treatment of 13.1, 20.3 and 44.6 months respectively (Stilgenbauer & Zenz, 2010).

In a single centre study, 33 of 112 patients who relapsed after initial treatment with FCR were retreated with FCR.

Table VI. Response definitions after treatment for patients with CLL.

Parameter	Group	CR	PR	PD
Lymphadenopathy	A	None > 1.5 cm	Decrease \geq 50%	Increase \geq 50%
Hepatomegaly	A	None	Decrease \geq 50%	Increase \geq 50%
Splenomegaly	A	None	Decrease \geq 50%	Increase \geq 50%
Blood Lymphocytes	A	$<4.0 \times 10^9/l$	Decrease \geq 50% from baseline	Increase \geq 50% over baseline
Marrow	A	Normocellular, < 30% lymphocytes, no B-lymphoid nodules	50% reduction in marrow infiltrate or B-lymphoid nodules	
Platelet count	B	$>100 \times 10^9/l$	$>100 \times 10^9/l$ or increase \geq 50% over baseline	Decrease of \geq 50% from baseline secondary to CLL
Haemoglobin	B	>110 g/l	>11 g/dl or increase \geq 50% over baseline	Decrease of >20 g/l from baseline secondary to CLL
Neutrophils	B	$>1.5 \times 10^9/l$	$>1500/\mu l$ or $>50\%$ improvement over baseline	

CR: complete response: all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR: partial response: at least two of the criteria of group A plus one of the criteria of group B have to be met; stable disease is absence of progressive disease (PD) and failure to achieve a PR. The International Workshop on Chronic Lymphocytic Leukaemia has recently agreed that blood lymphocytosis alone should not be a criterion for disease progression or relapse, based on the lymphocytosis observed in patients treated with BcR signalling inhibitors in the absence of disease progression.

Those patients who relapsed after 3 years had an overall response rate (ORR) and CR of 86% and 23%, respectively, compared to 54% and 0% for those relapsing within 3 years (Keating *et al*, 2009).

Previously untreated or relapsed patients with a TP53 abnormality who require therapy and those who relapse within 2 years of, or are refractory to purine analogue-based therapy regardless of biomarker results, are considered to have 'high risk' CLL. These patient groups have a poor outcome when treated conventionally and should be considered for alternative therapies as discussed in section 4.5.4.

Management of patients with no immediate indication for treatment

A diagnosis of stage A CLL is associated with an increased incidence of infections and auto-immune cytopenias. The quality of life of patients and family/partners may also be affected by a variety of factors including use of the term 'leukaemia', uncertainty about the long-term outlook, concerns about transmission of the disease to offspring and practical issues such as difficulties in obtaining insurance. These issues should be explored and addressed at presentation and regularly during the course of the disease (Shanafelt *et al*, 2007, 2009b; Evans *et al*, 2012). The issue of patient communication from both the haematologist's and patient's perspective is discussed on the UK CLL Forum website (www.ukcllforum.org).

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 (providing there are clear local guidelines for specialist referral), or in hospital clinics (medical, nurse practitioner or via teleclinics) depending on local arrangements.

A meta-analysis of 2048 patients in six trials of immediate treatment with chlorambucil plus or minus prednisolone *versus* deferred treatment showed no significant difference in 10-year-survival (CLL Trialists' Collaborative Group, 1999). The benefits of early *versus* delayed treatment using FCR, FR or lenalidomide in asymptomatic early stage patients with poor risk prognostic factors are currently being evaluated in randomized trials.

Recommendation

- **Treatment of early stage disease is not currently indicated (Grade A1).**

Treatment options

General considerations.

- Treatment options are provided based on fitness to tolerate FCR chemo-immunotherapy and whether patients are previously untreated or have relapsed or high-risk disease.

- The recommendations given below are largely based on the results of clinical trials, especially phase III studies. However, it is recognized that many elderly patients are excluded from trials due to co-morbidities.
- The inclusion of patients who may be either minimally or heavily pretreated and who may have either refractory or responsive disease, makes the results of many second line studies difficult to interpret.
- Clinical trials employing cladribine or pentostatin rather than fludarabine have not shown convincing evidence of improved efficacy over fludarabine and their use outside clinical trials is not recommended (Robak *et al*, 2006, 2010; Kay *et al*, 2007; Reynolds *et al*, 2008).
- BCSH guidelines recommend the use of irradiated blood products in the following situations: indefinitely in patients treated with a purine analogue, following bendamustine until more evidence emerges about the risk of transfusion-associated graft-*versus*-host disease, following alemtuzumab and for 3 months post-conditioning with chemotherapy or immunotherapy (6 months after total body irradiation) for patients undergoing autologous transplantation (Treleaven *et al*, 2011)
- Therapeutic agents with marketing authorisation for use in the UK, their licensed indications, current National Institute for Health and Clinical Excellence (NICE) and Scottish Medicines Consortium (SMC) guidance for the management of CLL and details of current National Cancer Research Institute (NCRI) CLL trials are available on the UK CLL Forum website (www.ukcllforum.org).
- A retrospective survey of the outcome of patients with CLL managed by either a haemato-oncologist specializing in CLL or in another haematological malignancy showed an improved OS for patients managed by CLL experts after adjusting for age, gender, stage and lymphocyte count at diagnosis (Shanafelt *et al*, 2012). This supports the UK model of discussing the management of patients with CLL, including those with Stage A disease, at a multidisciplinary team meeting attended by a haematologist experienced in the management of CLL.

Initial treatment of fit patients with no TP53 abnormality.

Table VII summarizes the results of recent phase III trials that showed an improved outcome for patients treated with FC compared to F or chlorambucil (Eichhorst *et al*, 2006; Catovsky *et al*, 2007; Flinn *et al*, 2007) and with FCR compared to FC (Hallek *et al*, 2010).

Phase II studies have demonstrated the efficacy of FR (Woyach *et al*, 2011), BR (Fischer *et al*, 2009) and FCMR (fludarabine + cyclophosphamide + mitoxantrone + rituximab) (Bosch *et al*, 2009) (Table VIII), and Phase III studies comparing these regimens with FCR are in progress.

Recommendation

- **FCR is recommended as initial therapy for previously untreated fit patients outside clinical trials (Grade A1).**

Table VII. Phase 3 studies of initial treatment of fit patients.

Study	Regimen	Patients (n)	Median age (years)	CR (%)	OR (%)	Median PFS (months)	Median OS (%)	Grade 3–4 neutropenia (%)
Eichhorst <i>et al</i> (2006)	FC	180	58	24	94	48	81 (3 years)	26
	F	182	59	7	83	20	80 (3 years)	56
Flinn <i>et al</i> (2007)	FC	141	61	23	74	32	NA	69
	F	137	61	5	59	19	NA	63
Catovsky <i>et al</i> (2007)	FC	196	65	38	94	43	54 (5 years)	56
	F	194	64	15	80	23	52 (5 years)	41
Hallek <i>et al</i> (2010)	FC	409	61	22	80	33	NA	21
	FCR	408	61	44	90	52	NA	34

CR, complete response; OR, overall response; PFS, progression-free survival; OS, overall survival; F, fludarabine; FC, fludarabine + cyclophosphamide; FCR, fludarabine + cyclophosphamide + rituximab; NA, not available.

Table VIII. Phase 2 studies of initial treatment for fit patients.

Study	Regimen	Patients (n)	Median age (years)	CR (%)	OR (%)	Median PFS (months)	Median OS (months)	Grade 3–4 neutropenia (%)
Byrd <i>et al</i> (2003) updated by Woyach <i>et al</i> (2011)	FR	104	63			42	85	
Bosch <i>et al</i> (2008)	FCM	69	NA	64	90	37	NA	10
Bosch <i>et al</i> (2009)	FCMR	72	60	82	93	NA	NA	13
Tam <i>et al</i> (2008)	FCR	300	57	72	95	80	77 (6 years)	
Lamanna <i>et al</i> (2009)	FCR (sequential)	36	59	61	89	43	71 (5 years)	NA
Wierda <i>et al</i> (2011)	FC O (low dose)	31	56	50	77	NA	NA	48
	FC O (high dose)	30		32	73	NA	NA	
Fischer <i>et al</i> (2009)	BR	117	64	33	91	NA	NA	15

CR, complete response; OR, overall response; PFS, progression-free survival; OS, overall survival; FR, fludarabine + rituximab; FCM, fludarabine + cyclophosphamide + mitoxantrone; FC, fludarabine + cyclophosphamide; FCR, fludarabine + cyclophosphamide + rituximab; O, ofatumumab; BR, bendamustine + rituximab; NA, not available.

• **Patients who progress after one cycle of FCR or who have stable disease after two cycles have high-risk disease and should be managed accordingly (section 4.5.5).**

Initial treatment of unfit patients with no TP53 abnormality.

Chlorambucil remains widely used in the UK for patients considered unfit for intensive therapy. Although there is no international consensus as to the optimal dose or duration of chlorambucil therapy, the highest response rate and longest PFS have been reported in the UK Leukaemia Research Fund (LRF) CLL4 trial in which chlorambucil was administered at a dose of 10 mg/m²/d for 7 d every 4 weeks initially for 6 months extending to 12 months, in patients still responding after 6 months treatment (Catovsky *et al*, 2011).

The results of phase 3 studies comparing single agent chlorambucil with other regimens are given in Table IX and show no benefit for single agent fludarabine over chlorambucil.

A recent phase III study randomized patients to chlorambucil or bendamustine (Knauf *et al*, 2009) and showed a higher response rate and longer PFS for the bendamustine arm. The ORR and PFS in the chlorambucil arm was lower

than in the UK LRF CLL4 trial but comparisons between the two studies are hampered by the use of different chlorambucil dose regimens and differing inclusion criteria.

Preliminary data from phase II studies are shown in Table X. A higher ORR (80% vs. 66%) was achieved with the combination of chlorambucil and rituximab compared to a historical control arm derived from patients receiving single agent chlorambucil in the UK CLL4 trial (Hillmen *et al*, 2010). A similarly high ORR of 91% was obtained in 117 patients, of whom 26% were over the age of 70 years, treated with bendamustine and rituximab (BR) (Fischer *et al*, 2009). Phase III trials of chlorambucil or bendamustine in combination with an anti-CD20 antibody are in progress.

In view of the efficacy of FC and FCR in CLL, small non-randomized phase II studies have evaluated dose-reduced regimens in patients considered unfit for full dose treatment. (Forconi *et al*, 2008; Smolej *et al*, 2010) Although high response rates with acceptable toxicity are achievable, larger randomized studies with prolonged follow up are necessary to evaluate this treatment approach (Mulligan *et al*, 2010).

Table IX. Phase 3 studies of initial treatment of patients unfit for FCR.

Study	Regimen	Patients (n)	Median age (years)	CR (%)	OR (%)	Median PFS (months)	Grade 3–4 neutropenia (%)
Rai <i>et al</i> (2000)	F	179	64	20	63	20	27
	Chlor	193	62	4	37	14	19
Catovsky <i>et al</i> (2007)	F	194	64	15	80	23	41
	Chlor	387	65	7	72	20	28
Eichhorst <i>et al</i> (2009)	F	93	71	7	72	19	12
	Chlor	100	70	0	51	18	12
Hillmen <i>et al</i> (2007)	A	149	59	24	83	15	41
	Chlor	148	60	2	55	12	25
Knauf <i>et al</i> (2009)	B	162	63	31	68	22	23
	Chlor	157	66	2	31	8	11

CR, complete response; OR, overall response; PFS, progression-free survival; FCR, fludarabine + cyclophosphamide + rituximab; F, fludarabine; Chlor, chlorambucil.

Table X. Phase 2 studies of initial treatment of patients unfit for FCR.

Study	Regimen	Patients (n)	Median age (years)	CR (%)	OR (%)	Median PFS (months)	Grade 3–4 neutropenia (%)
Hillmen <i>et al</i> (2010)	C+R	100	70	9	82	NA	39
Castro <i>et al</i> (2009)	HDMPR	28	65	32	96	30	3
Forconi <i>et al</i> (2008)	FC	14	71	83.5	100	48	28
Badoux <i>et al</i> (2011)	Lenalidomide	60		10	65	60	34

CR, complete response; OR, overall response; PFS, progression-free survival; FCR, fludarabine + cyclophosphamide + rituximab; C+R, cyclophosphamide + rituximab; HDMPR, high dose methylprednisolone + rituximab; FC, fludarabine + cyclophosphamide; NA, not available.

Recommendations (Grade B1)

- **Options for patients unfit for FCR include chlorambucil or bendamustine.**
- **Entry of patients into trials of chlorambucil or bendamustine in combination with anti CD20 antibodies is strongly encouraged.**
- **Further studies are required to determine the efficacy of dose-reduced FC or FCR.**

Management of relapsed CLL with no TP53 abnormality.

Patients who relapse and have not acquired a TP53 abnormality can be expected to respond to a further course of their initial therapy, although the PFS is usually shorter than after initial therapy and repeated courses often lead to drug resistance. However, re-treatment with the previous therapy is not recommended in patients whose initial treatment was sub-optimal or if a new treatment, shown to be superior to the initial therapy, becomes available.

The results of studies that include patients with relapsed disease are shown in Table XI. Specific recommendations for patients relapsing after FC or FCR and for patients relapsing after or refractory to chlorambucil, are provided below.

Relapse at least 2 years after fludarabine combination chemotherapy or chemo-immunotherapy—There are no phase III studies of patients relapsing after FC or FCR. A

non-randomized phase II study of FCR in 284 patients with relapsed CLL showed a higher CR rate and longer PFS and OS than seen in a historical cohort treated with FC. Seventy-eight out of two-hundred and eighty-four patients received prior therapy with regimens that included fludarabine and an alkylating agent. Thirteen per cent and 9% were refractory to fludarabine and chlorambucil respectively. The ORR was 73% with 42% CR + nodular PR (nPR) and the PFS was 19 months. The CR + nPR rate for fludarabine-responsive cases was 46% compared to 8% for fludarabine-refractory cases (O'Brien *et al*, 2001; Badoux *et al*, 2011).

A non-randomized phase II study of BR has shown response rates of 60% and 45% for relapsed or fludarabine-refractory patients, respectively, with an event-free survival (EFS) of 14.7 months. Only 2/14 patients with a 17p deletion responded (Fischer *et al*, 2008; Iannitto *et al*, 2011).

Recommendation (Grade B2)

- **Patients relapsing at least 2 years after FC, FCR or similar regimens who have not acquired a TP53 abnormality, remain fit enough for fludarabine-based treatment and in whom there is a clinical indication for treatment, should receive FCR.**
- **Further studies are required to evaluate the role of bendamustine in combination with an anti-CD20 antibody in fit patients with relapsed disease.**

Table XI. Treatment of relapsed/refractory CLL.

Study	Regimen	Patients (n)	Refractory Patients (%)	Median age (years)	Median number of prior treatments	CR (%)	OR (%)	Median PFS (months)	Median OS (months)	Grade 3–4 neutropenia (%)
Robak	FCR	276	0	63	1	24	70	30.6		89
<i>et al</i> (2010)	FC	276	0	62	1	13	58	20.6		84
Badoux	FCR	230	0	60	2	36	79	28	52	
<i>et al</i> (2011)	FCR	54	100 (F)			7	56	8	38	
	FC	114	29 (F)			23	68	11	21	
	FCR	67	100 (Chlor)			10	66	9	39	
Fischer	BR	78	28 (F)	67	2	9	59	15		23.1
<i>et al</i> (2011)										
Iannitto	B	22				32.5				
<i>et al</i> (2011)	BR	87	57	66	3	13.6	70	16	17	
Hillmen	FCMR	26				42	65	NA	NA	
<i>et al</i> (2011)	FCM	26				15	58	NA	NA	
Castro	R + HDMP	14	100 (F)	59	2	36	93	15	NA	
<i>et al</i> (2008)										
Dungarwalla	R + HDMP	14	100 (F)	62	2	14	93	7	20	
<i>et al</i> (2008)										
Elter	F	167	40	60	1	4	75	16.5	32.9	68
<i>et al</i> (2011)	FA	168	40	61	1	13	82	23.7	NR	59

CR, complete response; OR, overall response; PFS, progression-free survival; OS, overall survival; FCR, fludarabine + cyclophosphamide + rituximab; FC, fludarabine + cyclophosphamide; BR, bendamustine + rituximab; B, bendamustine; FCMR, fludarabine + cyclophosphamide + mitoxantrone + rituximab; FCM, fludarabine + cyclophosphamide + mitoxantrone; R + HDMP, rituximab + high dose methylprednisolone; F, fludarabine; FA, fludarabine + alemtuzumab; Chlor, chlorambucil; NA, not available; NR, not reached.

Relapse after or refractory to chlorambucil. Most patients who relapse after chlorambucil will respond to retreatment with chlorambucil.

The phase II trials of BR discussed in the previous section included elderly patients and the acceptable toxicity indicated that this regimen may be suitable for relapsed or refractory patients unfit for FCR.

The REACH study randomized patients relapsing predominantly after single agent alkylating or purine analogue therapy to FC v FCR and showed an improved ORR, CR and PFS in the FCR arm (Robak *et al*, 2010).

Recommendation (Grade B2)

- **Patients relapsing after chlorambucil can be retreated with chlorambucil.**
- **Entry into trials that include bendamustine or chlorambucil and an anti-CD20 antibody is strongly recommended.**
- **In the absence of a suitable trial, BR should be considered for patients refractory to chlorambucil.**
- **The minority of patients relapsing after chlorambucil who are fit enough to receive fludarabine-based therapy should be considered for FCR.**
- **Other options for patients who are refractory to chlorambucil and unable to tolerate myelosuppressive therapy include high dose steroids, alone or in combination with rituximab, and alemtuzumab.**

Management of High-risk CLL. Initial treatment—There have been no randomized studies specifically for patients with high risk CLL (*TP53* defect and/or failing fludarabine combination therapy within 2 years). The results of phase II and III studies using either FC, FCR, or alemtuzumab with or without high dose steroids and included previously untreated patients with a *TP53* abnormality are shown in Table XII. FCR and alemtuzumab are associated with similar response rates and PFS. However, combination therapy with alemtuzumab and pulsed high-dose glucocorticoids achieves response rates and PFS superior to those achieved with FCR or alemtuzumab alone. Consequently, alemtuzumab plus pulsed methylprednisolone or dexamethasone should be regarded as the induction regimen of choice. This regimen is associated with a significant risk of infection and meticulous attention should be paid to antimicrobial prophylaxis and supportive care. Routine antimicrobial prophylaxis with oral co-trimoxazole, aciclovir and itraconazole and monitoring for cytomegalovirus (CMV) reactivation is recommended.

As the duration of remission following alemtuzumab-containing regimens is relatively short, consolidation with allogeneic transplantation (see below) is recommended in suitable patients.

Treatment of relapsed/refractory disease—The results of studies of fludarabine-refractory CLL are shown in Table XIII. The outcome of fludarabine-refractory patients treated with chemotherapy is poor with a median OS of approximately

Table XII. Phase 2 and 3 studies of initial therapy for patients with *TP53* abnormality.

Study	Regimen	Patients (<i>n</i>)	CR (%)	OR (%)	Median PFS (months)	OS (%)
Hallek <i>et al</i> (2010)	FC	29	4	45	0 (2 years)	41 at 2 years
	FCR	22	19	71	11	NA
Hillmen <i>et al</i> (2007)	A	11		64	11	NA
Pettitt <i>et al</i> (2012)	A + HDMP	17	65	100	18.3	38.9 (median)
Stilgenbauer <i>et al</i> (2011)	A + Dex	30	20	97	16.9	NA

CR, complete response; OR, overall response; PFS, progression-free survival; OS, overall survival; FC, fludarabine + cyclophosphamide; FCR, fludarabine + cyclophosphamide + rituximab; A, alemtuzumab; A + HDMP, alemtuzumab + high dose methylprednisolone; A + Dex, alemtuzumab + dexamethasone; NA, not available.

Table XIII. Treatment of relapsed/refractory patients with high risk disease.

Study	Regimen	Patients (<i>n</i>)	Median number of prior treatments	CR (%)	OR (%)	Median PFS (months)	Median OS (months)	<i>TP53</i> abnormality (%)	Fludarabine Refractory (%)
Keating <i>et al</i> (2002)	A	93	3	2	33	4.7	16	N/A	100
Lozanski <i>et al</i> (2004)	A	36	3	6	31	NA	NA	42	81
Stilgenbauer <i>et al</i> (2009)	A	103	3	4	34	7.7	19.1	30	100
Pettitt <i>et al</i> (2012)	A + HDMP	22	NA	14	76	6.5	19	100	NA
Elter <i>et al</i> (2005)	A + F	36	2	31	83	13	NA		25
Wierda <i>et al</i> (2010)	O	59 (FA ref)	5	0	51	5.5	14.2	29	
		78 (BF ref)	4	2	44	5.5	17.4	18	
Badoux <i>et al</i> (2011)	CFAR	80	3	29	65	10.6	16.7	30 (46 patients tested)	39

CR, complete response; OR, overall response; PFS, progression-free survival; OS, overall survival; A, alemtuzumab; A + HDMP, alemtuzumab + high dose methylprednisolone; A + F/FA, alemtuzumab + fludarabine; O, ofatumumab; CFAR, cyclophosphamide + fludarabine + alemtuzumab + rituximab; BF, bendamustine + fludarabine; ref, refractory; NA, not available.

8 months. Alemtuzumab alone results in an ORR of about 30–35%. Combining alemtuzumab with high-dose steroids results in an improved ORR but the PFS and OS are nevertheless unsatisfactory.

Regimens that include fludarabine and alemtuzumab have activity in patients refractory to either agent alone but responses are not durable and the risk of infectious complications is high (Elter *et al*, 2005; Badoux *et al*, 2011).

As with the initial treatment of high-risk disease, the duration of remission following alemtuzumab-containing regimens is short and consolidation therapy, such as allogeneic transplantation (see below), is recommended in suitable patients. For patients for whom allogeneic transplantation is not an option, re-treatment with alemtuzumab should be considered in those patients who relapse more than 12 months after initial treatment (Fiegl *et al*, 2011).

Treatment options for patients who fail or relapse early after alemtuzumab-based therapy are limited. Active agents include ofatumumab, lenalidomide (Ferrajoli *et al*, 2008) and high-dose steroids with or without rituximab (Pilecky *et al*,

2011). Steroids given at conventional dose can provide useful short-term disease control and improve CLL-related symptoms. The choice of therapy depends on patient fitness, previous treatment and drug availability. In the registration study (Wierda *et al*, 2010), ofatumumab achieved an ORR of 58% in patients refractory to both fludarabine and alemtuzumab (double refractory) and 47% in patients with bulky, fludarabine-refractory CLL for whom alemtuzumab was considered inappropriate. The median PFS was approximately 6 months for both groups (Wierda *et al*, 2010). The effectiveness of ofatumumab was not influenced by bulky lymphadenopathy, prior rituximab exposure or refractoriness to FCR. The ORR was lower (14%) among patients with a 17p deletion in the bulky fludarabine-refractory group, but 41% in double refractory 17p deleted disease.

Role of radiotherapy—Radiotherapy should be considered for patients for whom chemo-immunotherapy has been ineffective or is contra-indicated and can provide effective palliation in cases with symptomatic bulky lymphadenopathy. Low

doses of external beam radiotherapy (2×2 Gy) can be highly effective in this situation and a higher dose (30 Gy in 2–3 Gy fractions) may be required in patients with transformed aggressive disease or those known to have a *TP53* abnormality (Lowry *et al*, 2011).

Recommendations (Grade B1/2)

- **The management of high-risk CLL is controversial and poses considerable therapeutic challenges. Accordingly, early input from a centre with a specialist interest in CLL is strongly recommended.**
- **Treatment for high-risk CLL should ideally be delivered as part of a clinical trial. Outside of trials, alemtuzumab in combination with pulsed high dose glucocorticoid is the treatment of choice. Meticulous attention should be paid to antimicrobial prophylaxis and supportive care.**
- **The use of alemtuzumab in combination with drugs other than steroids should be confined to clinical trials**
- **Subcutaneous alemtuzumab injection is associated with comparable efficacy and less toxicity in CLL and this has become the preferred route of administration**
- **Ofatumumab is the treatment of choice for patients with high-risk CLL who fail alemtuzumab. Other options include high-dose or conventional-dose glucocorticoids, lenalidomide or radiotherapy.**

The role of allogeneic transplantation

Allogeneic stem-cell transplantation provides the best opportunity of achieving long-term disease-free survival for patients with high-risk CLL, including those with *TP53* abnormalities. An European Group for Blood and Marrow Transplantation (EBMT) retrospective study of 44 transplants performed between 1995 and 2006 for 17p deleted CLL showed that about one-third of patients achieved long-term remission (Schetelig *et al*, 2008). In the German CLL Study Group CLL3X trial, the 4-year EFS was 42% and was similar for all genetic subtypes (Dreger *et al*, 2010), indicating that 17p deletion loses its adverse prognostic significance in this therapeutic context.

A comparison of registry data suggests that reduced intensity conditioning (RIC) transplants may be superior to myeloablative transplants – the reduction in disease control using a reduced intensity approach is more than compensated for by the reduction in treatment-related mortality. Recent data from the EBMT suggest that the outcomes following transplants from fully matched unrelated donors are identical to those following transplants from sibling donors and will increase the donor pool (Michallet *et al*, 2010). Analysis of prospective trials of allografting in CLL suggests that not being in remission has greater adverse prognostic significance than the number of lines of prior therapy (Delgado *et al*, 2009). Data from the Seattle group also clearly

identify the poorer outlook for both overall survival, EFS and non-relapse mortality in patients with co-morbidities (Sorrer *et al*, 2008).

The results of recent allogeneic transplant studies are given in Table XIV and current UK-CLL Forum and British Society for Bone Marrow Transplantation recommendations for allogeneic transplantation in CLL, which incorporate the EBMT consensus indications (Dreger *et al*, 2007), are shown in Table XV.

In view of the fact that CLL-type MBL is detectable in 3–5% of healthy adults and in 13–18% of siblings of patients with CLL (Rawstron *et al*, 2002; Marti *et al*, 2003; Del Giudice *et al*, 2009), the question arises as to the benefit of screening potential donors, especially family donors, pre-transplant. Information on the outcome of CLL patients whose donor had MBL is very limited and the risk of acquiring progressive CLL from the donor should be balanced against the prognosis of the potential transplant recipient, particularly if no alternative donor or other type of treatment is available (Hardy *et al*, 2007; Flandrin-Gresta *et al*, 2010; Herishanu *et al*, 2010). There is currently no national or international consensus on the need to screen potential donors for MBL. It would seem sensible to exclude donors with either early CLL or cMBL in whom the majority of B lymphocytes are clonal (Rawstron & Hillmen, 2010).

Recommendations

- **Allogeneic stem-cell transplantation should be considered as consolidation therapy for all fit patients with high-risk CLL and should ideally be performed in the setting of a secure remission. Suitable patients should be discussed with a transplant centre at the earliest opportunity (Grade B1).**
- **There is no consensus on the value of screening potential allograft donors for MBL. It would seem sensible to exclude donors with early CLL or cMBL (Grade C2).**

Consolidation/maintenance therapy

Antibody therapy. The observation that an MRD-negative remission is associated with prolonged PFS, both in previously untreated (Bosch *et al*, 2008; Tam *et al*, 2008) and relapsed cases (Moreton *et al*, 2005), has led to studies of additional treatment in patients with residual disease post-therapy.

The use of alemtuzumab following initial therapy with fludarabine-based regimens has led to an improved CR rate, MRD eradication and prolonged PFS, but the potential for infective complications necessitates careful attention to the timing of consolidation therapy and to antimicrobial prophylaxis and treatment (Schweighofer *et al*, 2009; Lin *et al*, 2010; Varghese *et al*, 2010; Wierda *et al*, 2011).

Table XIV. Outcome of patients following allogeneic transplantation.

Study	Patients (<i>n</i>)	Median age, years (range)	Transplant	Conditioning Regimen	Donor- related (%)	Extensive cGVHD (%)	PFS,% (median follow-up)	OS,% (median follow-up)
Pavletic <i>et al</i> (2005)	38	45 (26–59)	MA		0		30 (5 years)	33 (5 years)
Gribben <i>et al</i> (2005)	25	47 (29–55)	MA		100	50	24 (6 years)	55 (6 years)
Toze <i>et al</i> (2005)	30	48 (32–59)	MA		66		39 (5 years)	39 (5 years)
Schetelig <i>et al</i> (2003)	30	50 (12–63)	RIC	F.B.ATG	50	21	67(2 years)	73 (2 years)
Brown <i>et al</i> (2006)	43	53 (35–67)	RIC	F.B.	33	38	34 (2 years)	54 (2 years)
Khoury <i>et al</i> (2007)	39	57 (34–70)	RIC	FCR	90	58	44 (4 years)	48 (4 years)
Delgado <i>et al</i> (2008)*	41	52 (37–64)	RIC	F.M.A.	78	10	39 (3 years)	65 (3 years)
Delgado <i>et al</i> (2008)†	21	54 (34–64)	RIC	F.M	86	48	47 (3 years)	57 (3 years)
Sorrer <i>et al</i> (2008)	82	56 (42–64)	RIC	F.LD TBI	63	51	39 (5 years)	50 (5 years)
Schetelig <i>et al</i> (2008) (all patents had <i>TP53</i> loss)	44	54 (35–64)	RIC (89%)	Various	54	53	37 (3 years)	44 (3 years)
Dreger <i>et al</i> (2010)	90		RIC	FC +/- ATG			42 (4 years)	65 (4 years)

cGVHD, chronic graft-versus-host disease; PFS, progression-free survival; OS, overall survival; f/u, follow-up; MA, myeloablative; RIC, reduced intensity conditioning; F, fludarabine; B, bendamustine, M, mitoxantrone; A, alemtuzumab; ATG, antithymocyte globulin; FCR, fludarabine + cyclophosphamide + rituximab; LD TBI, low dose total body irradiation.

*Cohort 1 (41 patients) received alemtuzumab and cyclosporin for GVHD prophylaxis.

†Cohort 2 (21 patients) received cyclosporin plus methotrexate or mycophenolate for GVHD prophylaxis.

Preliminary data suggest that consolidation therapy with rituximab may prolong PFS (Hainsworth *et al*, 2003; Del Poeta *et al*, 2008; Bosch *et al*, 2010). The role of anti-CD20 antibody therapy and lenolidamide as maintenance/consolidation therapy are currently being evaluated in clinical trials.

Recommendation

- **Currently, consolidation and maintenance immunotherapy therapy should only be offered in clinical trials because the clinical benefit versus the risk of morbidity is still uncertain (Grade B2).**

Autologous transplantation. Recent phase III studies have evaluated the role of autologous stem cell transplantation in patients who achieve a good response to initial therapy. All showed prolongation of PFS or EFS compared to the observation arm with no improvement in OS (Michallet *et al*, 2011; Sutton *et al*, 2011; Brion *et al*, 2012). The majority of patients had not been exposed to rituximab and it is possible that gains of a similar magnitude might have been achieved with best modern induction therapy.

Recommendation

- **In the absence of an OS gain or evidence of improved quality of life, autografting is not recommended as part of standard care in CLL (Grade A1).**

Management of lymphomatous transformation

The outcome of CLL patients with lymphomatous transformation is significantly poorer than that of patients presenting with *de novo* lymphomas with a similar histology. Adverse risk factors include poor performance status, >2 prior therapies, >5 cm lymphadenopathy, clonal identity to the underlying CLL clone and loss or mutation of the *TP53* gene (Tsimberidou *et al*, 2006a; Rossi *et al*, 2011). There have been no randomized trials on the treatment of aggressive lymphomas that develop in CLL. The ORR for 130 patients treated at the MD Anderson Cancer Centre was 34% for those receiving intensive chemotherapy and 47% for those receiving chemotherapy and rituximab. The median survival was 8 months. Of the patients who achieved a remission, those who underwent allogeneic stem cell transplantation had a longer survival than those receiving no additional

Table XV. Indications for allogeneic stem cell transplantation.

Allogeneic transplantation is a reasonable treatment option for previously treated patients with poor risk features as defined below

European Group for Blood and Marrow Transplant (EBMT) 2006*	UK CLL Forum/British Society for Bone Marrow Transplants (BSBMT) Recommendations†
Non response or early relapse (within 12 months) after purine analogue containing therapy	Relapse within 6 months of purine analogue therapy
Relapse within 24 months after purine analogue combination therapy or treatment of similar efficacy, such as autologous transplantation	Relapse within 24 months of intensive therapy including purine analogue/alkylator combinations, chemo-immunotherapy or autologous transplantation
Patients with <i>TP53</i> loss/mutation requiring treatment	Patients with <i>TP53</i> loss/mutation ideally after maximal response to <i>TP53</i> independent therapy Patients not fulfilling the above criteria who are in second or subsequent relapse with at least one other commonly recognized adverse feature as follows: bone marrow failure according to Binet criteria, unmutated <i>IGHV</i> genes, high expression of ZAP70 or CD38, deletion of 11q

*Dreger *et al* (2007).

†<http://www.ukcllforum.org/CLL%20transplant%20guidelines.pdf>

therapy or those who underwent allogeneic or autologous transplantation for relapsed or refractory disease (Tsimberidou *et al*, 2006b). In a separate analysis of 18 patients who developed HL the ORR to 'Hodgkin like' chemotherapy was 44% (Tsimberidou *et al*, 2006a). The median OS was 0.8 years. More recently an ORR of 50% was achieved in 20 patients with lymphomatous transformation treated with a combination of Oxaliplatin, fludarabine, cytarabine and rituximab. The median response duration was 10 months (Tsimberidou *et al*, 2008).

Options are limited for patients unable to tolerate intensive therapy but palliation might be achieved using a high dose steroid regimen.

Recommendations

- **The diagnosis of lymphomatous transformation requires histological confirmation.**
- **Depending on the histological sub type of lymphomatous transformation, patients who are suitable for intensive therapy should receive regimens currently employed for either primary DLBCL or HL (preferably in the context of a clinical trial). Younger patients who achieve a**

good response are candidates for allogeneic stem cell transplantation (Grade B2).

Treatment of small lymphocytic lymphoma

Data on the optimal treatment of SLL is limited and patients are often included in studies that include other low grade B cell lymphomas rather than CLL. However, the biological similarities between SLL and CLL are so close that a similar response to treatment could be expected. This is supported by a single centre retrospective study of CLL and SLL that also showed a better outcome for both disorders when treated with regimens that included a nucleoside analogue and rituximab (Tsimberidou *et al*, 2007).

Indications for, and choices of, treatment are the same as for CLL. The rare patient in whom SLL is diagnosed following biopsy of an enlarged lymph node in the absence of detectable disease at any other site, may be offered local radiotherapy with curative intent.

Recommendation

- **SLL should be managed in the same manner as CLL (Grade B2).**

Autoimmune complications in CLL

Autoimmune complications are common in CLL, occurring in 10–20% of patients (Hodgson *et al*, 2011). These almost exclusively target blood cells, most commonly red blood cells. The diagnosis of autoimmune haemolytic anaemia (AIHA) is based on the presence of an isolated fall in haemoglobin accompanied by a positive DAT, a rise in reticulocyte count, bilirubin and LDH, and a fall in serum haptoglobins. Immune thrombocytopenic purpura (ITP) (Visco *et al*, 2008) is less common (2–5%) and may occur in conjunction with AIHA (Evans syndrome). There is no precise diagnostic test but a fall in the platelet count with no other cause for thrombocytopenia is suggestive. Pure red cell aplasia is rare, but under-recognized, presenting with a fall in haemoglobin an associated reticulocytopenia and a negative DAT. It is important to rule out viral infections [Epstein Barr virus (EBV), CMV and Parvovirus B19] in this disorder. For all auto-immune cytopenias full evaluation usually requires a bone marrow aspirate and trephine biopsy.

Risk factors for developing AIHA include; a positive DAT, advanced stage disease (Stage C), high white blood cell count, older age, male gender and poor prognostic markers (high B2M, unmutated *IGHV* genes, ZAP70+, CD38+) (Dearden *et al*, 2008; Moreno *et al*, 2010; Zanotti *et al*, 2010) and initiating treatment. The reported incidence of AIHA following specific regimens varies among studies but is lower for FC and FCR than for single agent chlorambucil and fludarabine. (Borthakur *et al*, 2007; Dearden *et al*, 2008;

Hallek *et al*, 2010). Data on the incidence of AIHA following bendamustine or BR is more limited but the risk appears to be low (Knauf *et al*, 2009; Fischer *et al*, 2011). Chemo-immunotherapy combinations are recommended for patients whose CLL requires treatment and who have a positive DAT or have had a previous immune cytopenia either unrelated to treatment or following alkylating agent/purine analogue therapy. There is little data to inform the subsequent treatment of patients whose immune cytopenia occurred during chemo-immunotherapy. Options include a switch from FCR to BR and the use of prophylactic immunosuppressive therapy (see below).

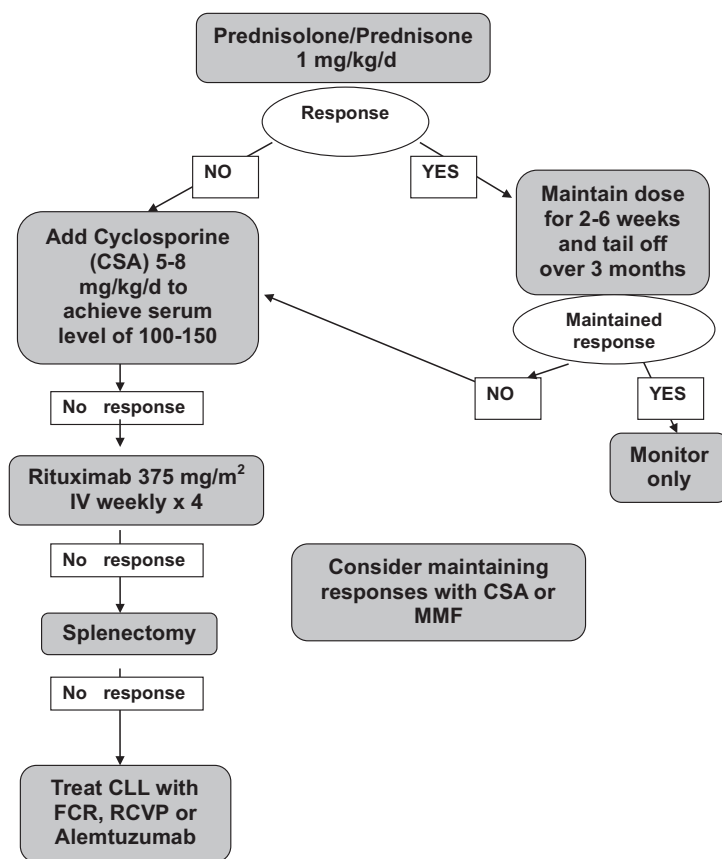
There are no controlled trials or systematic studies to inform the treatment of auto-immune cytopenias. A suggested algorithm is shown in Fig 1. The majority of patients respond to steroids but it can be difficult to withdraw treatment and immunosuppressive, steroid-sparing therapy, such as cyclosporine or azathioprine (Cortes *et al*, 2001), may be a helpful addition to allow this. Intravenous immunoglobulin (0.4 mg/kg/d for 5 d) can be used to induce rapid temporary elevation of counts, particularly in ITP. Splenectomy may be life-saving in patients with very vigorous uncontrolled

haemolysis or thrombocytopenia (Hill *et al*, 2004). Case reports indicate that thrombopoietin receptor agonists may be effective in patients with ITP (Koehrer *et al*, 2010; Sinisalo *et al*, 2011).

Low dose cyclophosphamide, rituximab (Ghazal, 2002; D’Arena *et al*, 2006) and alemtuzumab (Karlsson *et al*, 2007) have all been used successfully to treat refractory auto-immune cytopenias. Chemo-immunotherapy combinations may also be effective (Kaufman *et al*, 2009; Bowen *et al*, 2010). The presence of an auto-immune cytopenia is not in itself an indication to treat the CLL although it may arise in the context of disease progression and may not resolve without CLL-therapy. However, stage C disease due to bone marrow failure has a much worse prognosis than that due to AIHA and/or ITP and successful treatment of immune cytopenias often up-grades the CLL patient to Stage A or B (Zent *et al*, 2008; Moreno *et al*, 2010).

Recommendations (Grade B1)

- A bone marrow aspirate is usually required to confirm the diagnosis of auto-immune cytopenia.



Note : All patients with AIHA should receive folic acid 5-10 mg/d and red cell transfusion as necessary to maintain Hb >80 g/l

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.

- AIHA or ITP should be treated before deciding whether therapy for CLL is needed.
- First line therapy is prednisolone.
- Second line therapies for patients intolerant of or refractory to steroids, include cyclosporine, intravenous immunoglobulin (ITP), thrombopoietin mimetic agents (ITP), low-dose cyclophosphamide, rituximab, alemtuzumab and splenectomy.
- CLL treatment may be initiated to control recurrent or refractory AIHA/ITP. Rituximab –containing regimens are recommended in patients who do not have a TP53 abnormality.
- If AIHA/ITP develops during CLL treatment the same regimen should only be used again in that patient with extreme caution and if no effective alternative is available.
- Autoimmune neutropenia usually responds to granulocyte colony-stimulating factor (G-CSF).

Supportive care

Infective complications account for up to 50% of all CLL-related deaths. Risk factors for infection include advanced age, advanced stage, co-morbidities, a history of previous infections, hypogammaglobulinaemia, the number and nature of prior therapies and treatment responsiveness (Hensel *et al*, 2003).

Anti microbial prophylaxis

Detailed guidance on antimicrobial prophylaxis is beyond the scope of this guideline. Recent reviews on the prevention of infection in CLL (Morrison, 2010), and National Comprehensive Cancer Network guidelines on the prevention and treatment of cancer-related infections (NCCN.org) are recommended.

Important practice points are summarized below:

- Antimicrobial prophylaxis should be considered for patients with hypogammaglobulinaemia who develop recurrent bacterial infections. (Egerer *et al*, 2001; Hensel *et al*, 2003; Ravandi & O'Brien, 2006). This may be especially helpful in patients with bronchiectasis, in whom nebulized or low dose oral antibiotics such as azithromycin can reduce the incidence of recurrent infection.
- Anti-*Pneumocystis jirovecii* prophylaxis is recommended in patients requiring intensive and/or immunosuppressive treatment.
- Anti-herpes simplex virus and herpes zoster virus prophylaxis is recommended in patients requiring intensive and/or immunosuppressive treatment who are seropositive, have a low CD4 count or a history of previous herpes infections.
- The duration of anti-pneumocystis and herpes prophylaxis is controversial. Recommendations range from a minimum of 2 months post-therapy to awaiting a rise in CD4 count to $0.2 \times 10^9/l$.

- No prophylaxis is required in patients treated with alkylating agents or bendamustine. The use of prophylaxis is also controversial in fit patients receiving FC or FCR as first line therapy. Data from GCLLSG trials suggests that infection rates are low (Eichhorst *et al*, 2007).
- G-CSF should be administered according to American Society of Clinical Oncology guidelines (Smith *et al*, 2008).
- Patients receiving alemtuzumab should be monitored for CMV reactivation (O'Brien *et al*, 2006; Elter *et al*, 2009; Osterborg *et al*, 2009).
- Chemotherapy, immunotherapy with anti CD20 antibodies or alemtuzumab and transplantation may result in reactivation of hepatitis B and/or C virus infection. All patients with CLL receiving immunosuppressive therapy should be screened for evidence of previous hepatitis B or C infection. Patients positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antigen (HBCAg) may require antiviral treatment and should be managed jointly with a specialist in viral hepatitis (Artz *et al*, 2010).
- EBV reactivation should be considered in febrile CLL patients, especially those with high-risk disease (Rath *et al*, 2008).
- Progressive multifocal leucoencephalopathy (PML) has been reported as a rare complication in patients with chronic B cell lymphoproliferative disorders who have been treated with rituximab. This diagnosis should be considered in CLL patients who develop progressive confusion, weakness, poor motor coordination, speech or visual changes (Carson *et al*, 2009).

Recommendations (Grade A1)

- **All patients should be assessed for risk factors for infection and for current active infection prior to treatment.**
- **All patients receiving immunosuppressive therapy should be screened for hepatitis B and C infection pre-treatment.**

Immunoglobulin replacement therapy

Hypogammaglobulinaemia occurs in 20–70% of unselected patients with CLL. The incidence increases in patients with advanced disease stage, in those with a long disease duration and following immunosuppressive therapy (Hamblin & Hamblin, 2008; Morrison, 2010).

A systematic review and meta analysis of small randomized studies (Raani *et al*, 2009) conducted before the introduction of modern immunosuppressive therapy concluded that intravenous immunoglobulin replacement therapy in patients with a history of previous infection and/or low serum IgG levels, resulted in a significant reduction in both major infections and all clinically documented infections compared to a placebo group. There was no significant effect on overall mortality.

In the absence of recent randomized studies, recommendations for the use of immunoglobulin replacement in CLL are largely based on clinical experience and data from its use in primary immunodeficiencies (Egerer *et al*, 2001).

Indication. Recurrent or severe infection with encapsulated bacteria despite prophylactic oral antibiotic therapy in patients with a serum IgG < 5 g/l (excluding a paraprotein).

Department of Health guidelines on immunoglobulin use recommend that if a patient received unconjugated pneumococcal or other polysaccharide vaccine challenge many years ago and specific antibody levels are low, it would be reasonable to re-vaccinate before prescribing immunoglobulin replacement therapy (Wimperis *et al*, 2011).

There is no data in CLL to indicate whether immunoglobulin replacement is helpful in patients with recurrent bacterial infections, a normal serum IgG level and a poor serum antibody response to conjugated pneumococcal vaccines, although a subset have IgG subclass deficiency (Freeman *et al*, 2012).

Dose and route of administration. Immunoglobulin may be administered intravenously 3–4 weekly using an initial dose of 0.4 g/kg, or by weekly subcutaneous infusion, aiming for a trough level of 6–8 g/l after 4 months of treatment (Wasserman *et al*, 2009). The immunoglobulin dose should be adjusted according to clinical response and trough levels repeated after three doses. Higher trough levels may be of benefit in patients with underlying co-morbidities, particularly bronchiectasis (Bayrakci *et al*, 2005; Lucas *et al*, 2010; Maarschalk-Ellerbroek *et al*, 2011).

Monitoring. Patients should be reviewed regularly, especially in the first 12 months of treatment. The incidence and severity of infections and the type and antibiotic sensitivity of bacteria causing breakthrough infections should be recorded.

Routine blood tests should include annual hepatitis B (HBsAg) and C (hepatitis C polymerase chain reaction) screening, annual save serum sample and 3–4 monthly trough IgG levels.

Duration. Treatment should be stopped if there is no improvement in the frequency or severity of bacterial infections after 1 year (Provan *et al*, 2008). If a decision to stop immunoglobulin replacement is made, this should take place over the summer months and be reviewed prior to the onset of winter. Patients should continue on prophylactic antibiotics and be provided with an additional antibiotic to be taken should breakthrough infection develop.

Recommendations: Grade B2

- Immunoglobulin replacement therapy should be considered as a means of reducing the incidence of bacterial infections in patients with a low serum IgG level who have

experienced a previous major or recurrent minor bacterial infection despite optimal anti-bacterial prophylaxis.

- The goal should be to reduce the incidence of infection and the immunoglobulin dose should be adjusted accordingly.
- Patients should be reviewed regularly to evaluate the effectiveness of immunoglobulin replacement therapy and whether there is a continuing need for treatment.
- Patients who develop serious and/or recurrent infections despite antimicrobial prophylaxis and immunoglobulin replacement should be managed in conjunction with a microbiologist, infectious diseases specialist and/or immunologist.

Immunization

There are no randomized studies showing that vaccination of any type alters infection rates or outcomes from acquired infections in CLL. Antibody response rates to pneumococcal and influenza vaccines are lower in patients with CLL than in healthy controls (Sinisalo *et al*, 2003, 2007; Pollyea *et al*, 2010). However, vaccination is safe and some patients respond particularly if vaccinated early in the disease and if conjugate vaccines, particularly to *Streptococcus pneumoniae* (Prevenar) and *Haemophilus influenzae B* (Hib) are used (Hartkamp *et al*, 2001; Sinisalo *et al*, 2007). Seasonal flu vaccination should also be given and for H1N1, two doses are advised (De Lavallade *et al*, 2011). The timing of vaccination in relation to treatments such as anti-CD20 antibody therapy, which deplete normal B cells, is also important. Failure to achieve protective antibody levels following seasonal and HINI influenza vaccination have been noted in patients with CLL and lymphomas vaccinated 2 weeks prior to, during or up to 6 months post-rituximab. (Pollyea *et al*, 2010; Yri *et al*, 2011).

Advice on the use of specific vaccines is available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917.

Recommendations Grade B2

- Vaccination against *Streptococcus pneumoniae* (using a conjugate vaccine) and *Haemophilus influenzae* type B is recommended at diagnosis. Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if *S. pneumoniae* and Hib antibody levels have fallen.
- Annual vaccination against seasonal influenza and novel strains is recommended.
- Live vaccines such as polio, H. zoster and yellow fever should be avoided.
- Vaccinations should be avoided, if possible, 2 weeks prior to, during or up to 6 months after chemo-immunotherapy.

Suggested topics for audit

- Use of immunoglobulin replacement therapy.
- Vaccination policies.
- Screening for Hepatitis B/C pre chemo-immunotherapy.
- Screening for TP53 loss pre-treatment.
- Documentation of indication for treatment (according to IWCLL/National Cancer Institute guidance) in patient records.

Key recommendations

- Patients should be screened for a TP53 abnormality pre-treatment (if they are candidates for agents that act through TP53-independent mechanisms)
- FCR is recommended for fit, previously untreated or relapsed patients who require treatment and who have not entered a clinical trial.
- Alemtuzumab (with pulsed high dose steroids) should be considered for previously untreated or relapsed patients with a TP53 abnormality and those with fludarabine-refractory disease who require treatment.
- Suitable patients with poor risk factors such as a TP53 abnormality and those who relapse early after intensive therapy should be considered for allogeneic transplantation.
- In view of the increasing number of new agents showing significant activity in phase 2 trials, and the extensive portfolio of trials now available in the UK, patients

should be offered entry into clinical trials wherever possible.

Disclaimer

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