

Guidelines on the diagnosis, investigation and management of Chronic Lymphocytic Leukaemia

British Committee for Standards in Haematology

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Introduction

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. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH (British Committee for Standards in Haematology) 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.
A list of commonly used abbreviations can be found in appendix 1.
approach.

Guideline update

This guideline replaces the previous BCSH guideline on chronic lymphocytic leukaemia published in 2004 and should be read in conjunction with the IWCLL guidance published in 2008.

Major changes since last guideline

- *The diagnosis of CLL now requires a minimum clonal B cell lymphocytosis of $>5 \times 10^9/l$.*
- *Two Phase 3 trials have shown that FCR is superior to FC in previously untreated patients and to alkylating agent or purine analogue monotherapy in relapsed disease.*

- *Poor outcome following FC and FCR is strongly associated with a TP53 abnormality, supporting the screening for TP53 loss pre treatment and the use of agents that act through p53 independent mechanisms in these patients.*

Summary of key recommendations.

- *Patients should be screened for a TP53 abnormality pre-treatment (if they are candidates for agents that act through p53 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 or without 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.*

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1 Abbreviations

1 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. 11% of patients are diagnosed under the age of 55 years (Howlander *et al*, 2011). Epidemiological surveys have shown a 7 fold 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 (Crowther-Swanepoel *et al*, 2010;Di Bernardo *et al*, 2008;Enjuanes *et al*, 2008).

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 HSC transplant donors) or for genetic susceptibility. (GRADE B1)

2 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 Smlg, 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 (MBL) ie those cases of MBL with a lymphocytosis detectable on a routine FBC, and small lymphocytic lymphoma (SLL) share a common immunophenotype, lymphocyte morphology and /or histology and similar biological features (Gibson *et al*, 2011; Hallek *et al*, 2008; Marti *et al*, 2005; Muller-Hermelink *et al*, 2008; Rawstron & Hillmen, 2010)). Distinguishing features are shown in Table 1.

3 CLINICAL AND LABORATORY EVALUATION

3.1 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 2) and determine whether B symptoms (fever, weight loss, profound lethargy and night sweats) and cytopenias are CLL-related, due to marrow infiltration, immune destruction or hypersplenism, or have an alternative cause.

3.2 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. HIV testing should be performed according to UK national guidelines (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 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 (Eichhorst *et al*, 2011; Hallek *et al*, 2008; Norin *et al*, 2010).. 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 immunotherapy 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)

3.3 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 (Rossi *et al*, 2008; Rossi *et al*, 2009; Tsimberidou & Keating, 2005). Histological appearances resemble diffuse large B cell lymphoma in approximately 80% of cases and Hodgkin's lymphoma in the remainder. Clinical features suggestive of lymphomatous transformation include bulky (>5cms) lymphadenopathy, rapid nodal enlargement, the appearance of extra nodal disease, the development of B symptoms and marked elevation of LDH. Since lymphomatous transformation may be localised, biopsy should be directed to the most suspicious clinical site. PET/CT (bloggs joe *et al*) 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)

3.4 Assessing Prognosis

The prognosis of patients with CLL is dependent on a variety of patient, disease and treatment -related factors (Table 3). Disease-related factors include biomarkers able to predict prognosis and those able to predict response to specific treatments.

3.4.1 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 (Binet *et al*, 1977; Rai *et al*, 1975). Adding simple clinical and laboratory parameters such as age, gender, lymphocyte count, lymphocyte doubling time and serum beta 2 microglobulin (B2M) to clinical stage improves the prediction of overall survival (Shanafelt *et al*, 2009b; Wierda *et al*, 2007) and time to first treatment in early stage CLL (Bulian *et al*, 2011; Molica *et al*, 2010).

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 recognise 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)

3.4.2 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 FISH (Gonzalez *et al*, 2011;Oscier *et al*, 2010;Stilgenbauer *et al*, 2009;Zenz *et al*, 2010;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 overall survival (OS), when treated with an alkylating agent, purine analogue, bendamustine, mitoxantrone and rituximab alone or in combination (Table 4). In contrast, *TP53* status has much less effect on the outcome of patients treated with agents such as alemtuzumab, that kill CLL cells through a p53-independent mechanism.

Unmutated IGHV genes, use of the stereotypic VH-3-21 gene, deletion of 11q and a raised B2M, independent of clinical stage, also correlate with reduced PFS and OS, in clinical trials of alkylating agent and purine analogue treatment (Oscier *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. However it is likely that this will be superseded by newer technologies able to detect *TP53* mutations as well (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)

4 MANAGEMENT

4.1 Indications for Treatment.

Patients with active disease, as defined in the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidelines, usually benefit from anti leukaemic therapy (Table 5). These criteria apply to both previously untreated and to relapsed patients. Neither a high lymphocyte count, in the absence of a rapid lymphocyte doubling time 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.

4.2 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.

4.2.1 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 CIRS score may be helpful, but none of the currently used scores is CLL-specific and careful assessment of individual patients remains paramount (Extermann *et al*, 1998; Miller *et al*, 1992). Although the outcome of patients over the age of 65-70 years entered into clinical trials of FC and FCR, is 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).

4.2.2 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 6 cycles of treatment providing toxicity is acceptable.

4.3 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 6. 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 either <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. Those patients who relapsed after 3 years had an

overall response rate (ORR) and CR of 86% and 23% 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

4.4 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; Shanafelt *et al*, 2009a; Evans *et al*, 2011). 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 vs. deferred treatment showed no significant difference in 10 years 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 randomised trials.

Recommendation

Treatment of early stage disease is not currently indicated (GRADE A1)

4.5 Treatment Options

4.5.1 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 recognised 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 (Kay *et al*, 2007; Reynolds *et al*, 2008; Robak *et al*, 2006; Robak *et al*, 2010).
- 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* 2010)
- Therapeutic agents with marketing authorisation for use in the UK, their licensed indications, current NICE and SMC guidance for the management of CLL and details of current NCRI CLL trials are available on the UK CLL Forum website.
- A retrospective survey of the outcome of patients with CLL managed by either a haemato-oncologist specialising 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*, 2011). This supports the UK model of discussing the management of patients with CLL, including those with Stage A disease, at an MDT meeting attended by a haematologist experienced in the management of CLL.

4.5.2 Initial treatment of fit patients with no TP53 abnormality

Table 7 summarises the results of recent phase III trials which show an improved outcome for patients treated with FC compared to F or chlorambucil (Catovsky *et al*, 2007; Eichhorst *et al*, 2006; 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 (Bosch *et al*, 2009) (Table 8), 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)

Patients who progress after 1 cycle of FCR or who have stable disease after 2 cycles have high risk disease and should be managed accordingly (section 4.5.5)

4.5.3 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 LRF CLL4 trial in which chlorambucil was administered at a dose of 10 mg/m²/day for 7 days 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 9 and show no benefit for single agent fludarabine over chlorambucil.

A recent phase III study randomised 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 10. A higher overall response rate (80% v 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 overall response rate of 91% was obtained in 117 patients, of whom 26% were over the age of 70 years, treated with bendamustine and rituximab (Fischer *et al*, 2009). Phase III trials of chlorambucil or bendamustine in combination with an antiCD20 antibody are in progress.

In view of the efficacy of FC and FCR in CLL, small non randomised 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 randomised studies with prolonged follow up are necessary to evaluate this treatment approach (Mulligan *et al*, 2010).

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

4.5.4 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 11. 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 randomised 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. 78/284 patients received prior therapy with regimens that included fludarabine and an alkylating agent. 13% and 9% were refractory to fludarabine and chlorambucil respectively. The ORR was 73% with 42% CR + nPR. PFS was 19 months The CR + nodular PR (nPR) rate for fludarabine responsive cases was 46% compared to 8% for fludarabine refractory cases (Badoux *et al*, 2011;O'Brien *et al*, 2001)

A non randomised phase II study of bendamustine and rituximab has shown response rates of 60% and 45% for relapsed or fludarabine-refractory patients respectively, with an event free survival 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

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 randomised 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 which 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.

4.5 5 Management of High-risk CLL

Initial treatment

There have been no randomised 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 which included previously untreated patients with a *TP53* abnormality are shown in Table 12. 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 CMV reactivation is recommended.

Since 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 13. The outcome of fludarabine-refractory patients treated with chemotherapy is poor with a median OS of approximately 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 (Badoux *et al*, 2011; Elter *et al*, 2005).

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, 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 R-FC. 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 x 2Gy) 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

Since subcutaneous alemtuzumab injection is associated with comparable efficacy and less toxicity in CLL, 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.

4.6 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 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 GCLLSG 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 TRM. 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 also clearly identify the poorer outlook for both overall survival, EFS and NRM in patients with co-morbidities (Sorró *et al*, 2008).

The results of recent allogeneic transplant studies are given in Table 14 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 15.

In view of the fact that CLL-type monoclonal B cell lymphocytosis (MBL) is detectable in 3-5% of healthy adults and in 13-18% of siblings of patients with CLL (Marti *et al*, 2003; Rawstron *et al*, 2002; Del, I *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; Herishanu *et al*, 2010; Flandrin-Gresta *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 clinical MBL 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 clinical MBL (GRADE C2)

4.7 Consolidation / Maintenance therapy

4.7.1 Antibody therapy

The observation that an MRD negative remission is associated with prolonged progression free survival 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 (Lin *et al*, 2010; Schweighofer *et al*, 2009; Varghese *et al*, 2010; Wierda *et al*, 2011).

Preliminary data suggest that consolidation therapy with rituximab may prolong PFS (Bosch *et al*, 2010; Del Poeta G. *et al*, 2008; Hainsworth *et al*, 2003). 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 as the clinical benefit versus the risk of morbidity is still uncertain (GRADE B2).

4.7.2 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 show prolongation of progression or event-free survival compared to the observation arm with no improvement in OS (Brion *et al*, 2011; Michallet *et al*, 2011; Sutton *et al*, 2011). 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 overall survival gain or evidence of improved quality of life, autografting is not recommended as part of standard care in CLL (GRADE A1).

4.8 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, >5cms lymphadenopathy, clonal identity to the underlying CLL clone and loss or mutation of the *TP53* gene (Rossi *et al*, 2011; Tsimberidou *et al*, 2006a). There have been no randomised trials on the treatment of aggressive lymphomas developing in CLL. The overall response rate 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 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 Hodgkin's lymphoma the overall response rate to "Hodgkin like" chemotherapy was 44% (Tsimberidou *et al*, 2006a). The median overall survival was 0.8 years. More recently an overall response rate 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 diffuse large B cell lymphoma or Hodgkin's lymphoma (preferably in the context of a clinical trial). Younger patients who achieve a good response are candidates for allogeneic stem cell transplantation (GRADE B2).

4.9 Treatment of small lymphocytic lymphoma

Data on the optimal treatment of SLL is limited and patients are often included in studies which 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 which 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. Rare patients 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).

5 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 thrombocytopenia (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-recognised, presenting with a fall in haemoglobin an associated reticulocytopenia and a negative DAT. It is important to rule out viral infections (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 WBC, older age, male gender and poor prognostic markers (high B2M, unmutated IGVH 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;2008;Dearden *et al*, 2008;Hallek *et al*, 2010). Data on the incidence of AIHA following B or BR is more limited but the risk appears to be low (Fischer *et al*, 2011;Knauf *et al*, 2009). 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 Figure 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/day for 5 days) 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 (D'Arena *et al*, 2006;Ghazal, 2002) and alemtuzumab (Karlsson *et al*, 2007) have all been used successfully to treat refractory auto-immune cytopenias. Chemo-immunotherapy combinations may also be effective (Bowen *et al*, 2010;Kaufman *et al*, 2009). 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 (Moreno *et al*, 2010;Zent *et al*, 2008).

Recommendations (GRADE B1)

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

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 GCSF.

6 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).

6.1 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 (2009) are recommended.

Important practice points are summarised below:

- Antimicrobial prophylaxis should be considered for patients with hypogammaglobulinaemia who develop recurrent bacterial infections. (Egerer *et al*, 2001; Hensel *et al*, 2003; Ravandi and O'Brien 2006). This may be especially helpful in patients with bronchiectasis, in whom nebulised 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 HSV and HZV 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 200/mcl.
- 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).
- GCSF should be administered according to ASCO guidelines.
- Patients received alemtuzumab should be monitored for CMV reactivation (Elter *et al*, 2009; O'Brien *et al*, 2006; 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 HBSAg or 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.

6.2 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 and Hamblin 2008; Morrison *et al*, 2010).

A systematic review and meta analysis of small randomised studies (Raanani *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 randomised 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 <5g/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 6-8g/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 3 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 PCR) 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 infections 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.

6.3 Immunisation.

There are no randomised 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; Pollyea *et al*, 2010; Sinisalo *et al*, 2007). However, vaccination is safe and some patients respond particularly if vaccinated early in the disease (Hartkamp *et al*, 2001; Sinisalo *et al*, 2007) and if conjugate vaccines, particularly to *Streptococcus pneumoniae* (Prevenar) and *Haemophilus influenzae b* (Hib) are used (Hartkamp *et al*, 2001; Sinisalo *et al*, 2001). Seasonal flu vaccination should also be given and for H1N1 two doses are advised (deLavallade H. *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 H1N1 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 Hep B/C pre chemo-immunotherapy

Screening for TP53 loss pre-treatment

Documentation of indication for treatment (according to IWCLL/NCI guidance) in patient records

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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

Table 1

Staging Systems in CLL

BINET Stage		Features
A		< 3 lymphoid areas*
B		> 3 lymphoid areas
C		haemoglobin <100g/l or platelets <100x10 ⁹ /l
RAI Stage	Risk group	
0	Low	lymphocytosis only
I		lymphadenopathy
II	Intermediate	hepatomegaly or splenomegaly + lymphocytosis
III / IV	High	haemoglobin <110g/l or platelets <100x10 ⁹ /l

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

Table 2

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
	Biomarkers
Treatment related:	Type of treatment
	Response/toxicity
	MRD status.

Table 3

Incidence of *TP53* abnormalities in CLL

Study	Number of patients	Patient Characteristics	% with <i>TP53</i> Mutation	% with 17p loss	% with <i>TP53</i> mutation without 17p loss	Outcome
(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 German CLLSG: CLL4 trial.	328	At trial entry FVFC	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 Ch 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 German CLLSG: 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 German CLLSG: CLL2H trial		F refractory treated with Alemtuzumab	37	32.3	12.1	No report of <i>TP53</i> mutation or 17p loss on outcome

NA;not available

Table 4

Indications for Treatment

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia 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 less than 6 months. In patients with initial blood lymphocyte counts of less than $30 \times 10^9/L$ 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 (ECOG) PS 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.

Table 5

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	< 4000/ μ 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	> 100.000/ μ l	> 100.000/ μ l or increase \geq 50% over baseline	Decrease of \geq 50% from baseline secondary to CLL
Haemoglobin	B	> 11.0 g/dl	> 11 g/dl or increase \geq 50% over baseline	Decrease of > 2 g/dl from baseline secondary to CLL
Neutrophils	B	>1500/ μ l	>1500/ μ l or >50% improvement over baseline	

*CR : all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR : 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. The IWCLL 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

Table 6

Phase 3 studies of initial treatment of Fit Patients

Study	Regimen	Number of patients	Median age (yrs)	CR (%)	OR (%)	Median PFS (months)	Median OS (%)	Grade 3-4 neutropenia (%)
Eichorst et al. 2006	FC	180	58	24	94	48	81 (3yrs)	26
	F	182	59	7	83	20	80 (3yrs)	56
Flinn et al. 2007	FC	141	61	23	74	32	NA	69
	F	137	61	5	59	19	NA	63
Catovsky et al. 2007	FC	196	65	38	94	43	54 (5yrs)	56
	F	194	64	15	80	23	52 (5yrs)	41
Hallek et al. 2010	FC	409	61	122	80	33	NA	21
	FCR	408	61	44	90	52	NA	34

NA: not available

Table 7

Phase 2 Studies of initial treatment for fit patients

Study	Regimen	Number of patients	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	N/A	64	90	37	N/A	10
Bosch <i>et al</i> . 2009	FCMR	72	60	82	93	N/A	N/A	13
Tam <i>et al</i> . 2008	FCR	300	57	72	95	80	77 (6yrs)	
Lamanna <i>et al</i> . 2009	FCR (sequential)	36	59	61	89	43	71 (5yrs)	N/A
Wierda <i>et al</i> . 2011	FC O (low dose)	31	56	50	77	N/A	N/A	48
	FC O (high dose)	30		32	73	N/A	N/A	
Fisher <i>et al</i> 2009	BR	117	64	33	91	N/A	N/A	15

N/A; not available

Table 8

Phase 3 studies of initial Treatment of patients unfit for FCR

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

Table 9

Phase 2 studies of initial treatment of Patients unfit for FCR

Study	Regimen	Number of patients	Median age	CR (%)	OR (%)	Median PFS (months)	Grade 3-4 Neutropenia (%)
Hillmen et al. 2010	CR	100	70	9	82	N/A	39
Castro et al. 2009	HDMPR	28	65	32	96	30	3
Forconi et al. 2008	FC	14	71	83.5	100	48	28
Badoux et al. 2011	Len	60		10	65	60	34

N/A; not available

Table 10

Treatment of Relapsed/Refractory CLL

Study	Regimen	Number of patients	Refractory Patients (%)	Median age	Median no of prior treatments	CR (%)	OR (%)	Median PFS (months)	Median OS (months)	Grade 3-4 neutropenia (%)
Robak et al. 2010	FCR	276	0	63	1	24	70	30.6		89
	FC	276	0	62	1	13	58	20.6		84
Badoux et al. 2011	FCR	230	0	60	2	36	79	28	52	
	FCR	54	100 (F)			7	56	8	38	
	FC	114	29 (F)			23	68	11	21	
	FCR	67	100 (Ch)			10	66	9	39	
Fisher et al. 2011	BR	78	28(F)	67	2	9	59	15		23.1
Iannitto et al. 2011	B	22	57	66	3	32.5	70	16	17	
	BR	87				13.6				
Hillmen et al. 2011	FCMR	26				42	65	N/A	N/A	
	FCM	26				15	58	N/A	N/A	
Castro et al.2008	R + HDMP	14	100(F)	59	2	36	93	15	N/A	
Dungerwalla et al 2008	R + HDMP	14	100(F)	62	2	14	93	7	20	
Elter et al. 2011	F	167	40	60	1	4	75	16.5	32.9	68
	FA	168	40	61	1	13	82	23.7	Not reached	59

NA; not available

Table 11

Study	Regimen	Number of patients	CR (%)	OR (%)	Median PFS (months)	OS (%)

Hallek et al 2010	FC	29	4	45	0(2yrs)	41 at 2yrs
	FCR	22	19	71	11	N/A
Hillmen et al 2007	A	11		64	11	N/A
Pettitt et al. 2012	A + HDMP	17	37	100	18.3	38.9 (median)
Stilgenbauer et al. 2011	A + Dex	30	20	97	16.9	N/A

Table 12

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

Treatment of relapsed/refractory patients with High Risk disease

Study	Regimen	Number of patients	Median no of prior treatments	CR (%)	OR (%)	Median PFS (months)	Median OS (months)	TP53 abnormality (%)	Fluda Refractory (%)
Keating et al. 2002	A	93	3	2	33	4.7	16	N/A	100
Lozanski et al 2004	A	36	3	6	31	N/A	N/A	42	81
Stilgenbauer et al.2009	A	103	3	4	34	7.7	19.1	30	100
Pettitt et al. 2012	A + HDMP	22	NA	14	76	6.5	19	100	NA
Elter et al 2005	A + F	36	2	31	83	13	N/A		25
Wierda et al. 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 et al 2011	CFAR	80	3	29	65	10.6	16.7	30 (46pts tested)	39

ref = refractory

Table 13

Outcome of patients following allogeneic transplantation

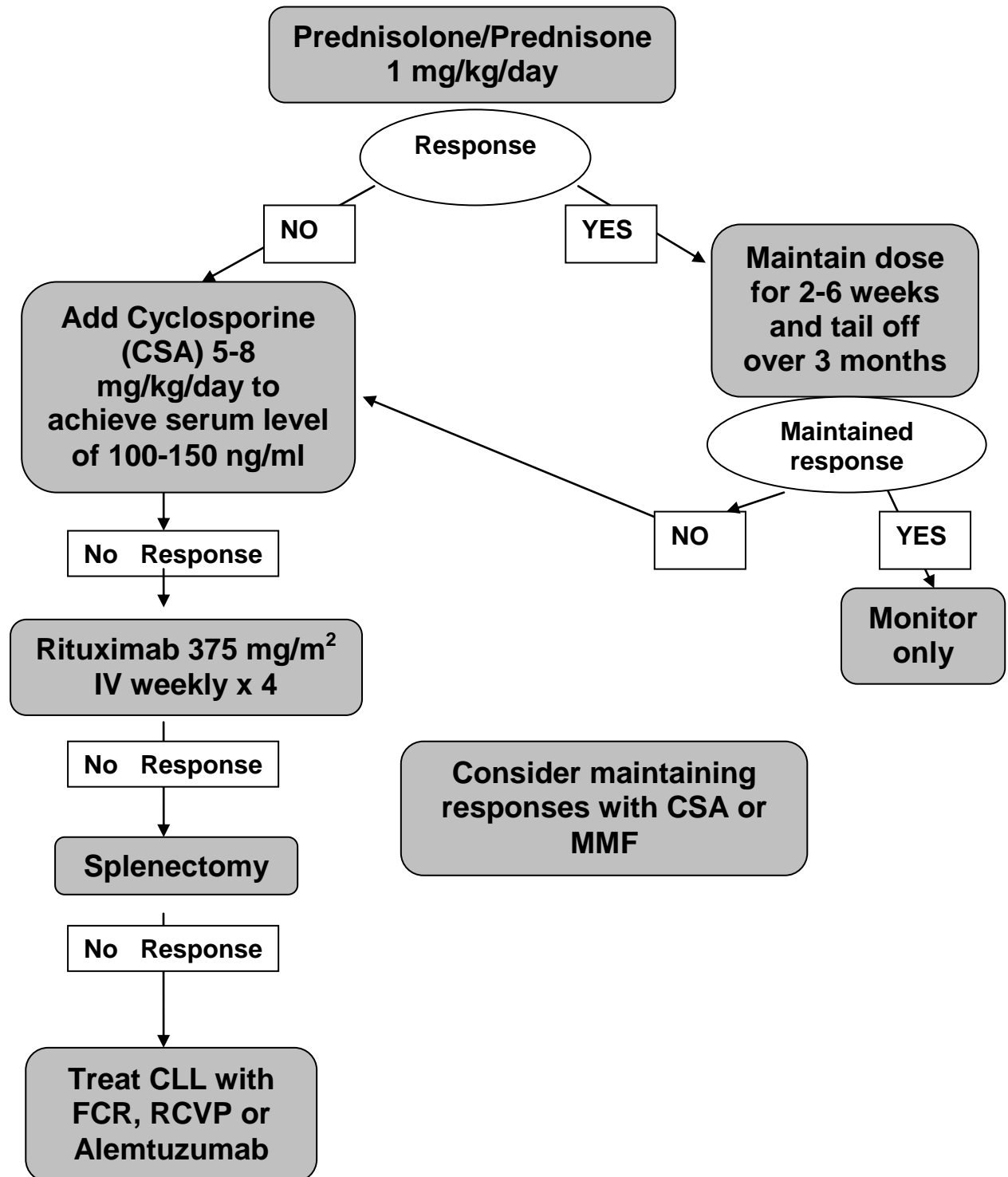
Study	Number of patients	Median age	Transplant	Conditioning Regimen	Donor % related	% extensive CGVHD	PFS % ()median f/u	OS % ()median f/u
Pavletic et al. 2005	38	45(26-59)	M/A		0		30 (5yrs)	33 (5yrs)
Gribben et al. 2005	25	47 (29-55)	M/A		100	50	24 (6yrs)	55 (6yrs)
Toze et al. 2005	30	48 (32-59)	M/A		66		39 (5yrs)	39 (5yrs)
Schetelig et al. 2003	30	50 (12-63)	RIC	F.B.ATG	50	21	67(2yrs)	73 (2yrs)
Brown et al. 2006	43	53 (35-67)	RIC	F.B.	33	38	34 (2yrs)	54 (2yrs)
Khoury et al. 2007	39	57 (34-70)	RIC	FCR	90	58	44 (4yrs)	48 (4yrs)
Delgado et al. 2008	41	52 (37-64)	RIC	F.M.A.	78	10	39 (3yrs)	65 (3yrs)
Delgado et al. 2008	21	54 (34-64)	RIC	F.M	86	48	47 (3yrs)	57 (3yrs)
Sorror et al. 2008	82	56 (42-64)	RIC	F.LD TBI	63	51	39 (5yrs)	50 (5yrs)
Schetelig et al. 2008 (all pts had TP53 loss)	44	54 (35-64)	RIC (89%)	Various	54	53	37 (3yrs)	44 (3yrs)
Dreger et al. 2010	90		RIC	FC +/- ATG			42 (4yrs)	65 (4yrs)

Table 14

Indications for allogeneic stem cell transplantation	
Allogeneic transplantation is a reasonable treatment option for previously treated patients with poor risk features as defined below:	
<u>European Group for Blood and Marrow Transplant (EBMT) 2006</u>	<u>UK CLL Forum /BSBMT Recommendations</u>
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 recognised 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.

Table 15

Figure 1: Treatment Algorithm for AIHA/ITP



Note : All patients with AIHA should receive folic acid 5-10 mg/day and red cell transfusion as necessary to maintain Hb >8 g/dl

Adapted from Dearden ASH Education Supplement 2008

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APPENDIX 1

CLL Guideline Abbreviations

Diseases

CLL	Chronic Lymphocytic Leukaemia
SLL	Small Lymphocytic Lymphoma
MBL	Monoclonal B cell Lymphocytosis
RS	Richter's Syndrome
DLBCL	Diffuse Large B Cell Lymphoma
HL	Hodgkin's Lymphoma
AIHA	Auto-immune Haemolytic Anaemia
ITP	Immune Thrombocytopenic Purpura
PRCA	Pure Red Cell Aplasia

Investigations

DAT	Direct Antiglobulin Test
LDT	Lymphocyte Doubling Time
B2M	Beta 2 Microglobulin
FISH	Fluorescence In Situ Hybridisation
IGHV	Immunoglobulin Heavy Chain Variable Region Gene

Outcome Measures

OR(R)	Overall Response (Rate)
CR	Complete Response
PR	Partial Response
NR	No Response
PFS	Progression Free Survival
MRD	Minimal Residual Disease
TRM	Treatment Related Mortality

Treatments

B	Bendamustine
Chlor	Chlorambucil
C	Cyclophosphamide
F	Fludarabine
M	Mitoxanthrone
A	Alemtuzumab
O	Ofatumumab
R	Rituximab
Dex	Dexamethasone
HDMP	High Dose Methylprednisolone

P	Prednisolone
FC	Fludarabine + Cyclophosphamide
FCR	Fludarabine + Cyclophosphamide + Rituximab
BR	Bendamustine + Rituximab
RIC	Reduced Intensity Conditioning

Antimicrobial Prophylaxis / Treatment

CMV	Cytomegalovirus
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface antigen
HBcAb	Hepatitis B Core Antibody
HCV	Hepatitis C Virus
HSV	Herpes Simplex Virus
IVIg	Intravenous Immunoglobulin
VZV	Varicella Zoster Virus
PML	Progressive Multifocal Leukoencephalopathy

Others

CIRS(-G)	Cumulative Illness Rating Scale (-Geriatric)
GCLLSG	German CLL Study Group
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Clinical Excellence
SMC	Scottish Medicines Consortium
IWCLL	International Workshop on CLL
MDT	Multidisciplinary team