GUIDELINES FOR THE MANAGEMENT OF CLL AND PLL

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Contents

This document should be read in conjunction with the British Committee for Standards in Haematology (BCSH – 2003), National Comprehensive Cancer Network (NCCN) for management of non-Hodgkin's Lymphoma (2009) and International Working Party on CLL (IwCLL – 2008) guidelines. The BCSH guidelines are currently being revised and an updated version is expected in late 2011.

1.0 Investigations at diagnosis and diagnostic criteria

Recommended investigations at diagnosis:

- FBC, blood film and reticulocyte count
- Renal function, liver function, urate and serum immunoglobulins
- Direct antiglobulin test (DAT/DCT)
- Immunophenotyping
- Clinical staging (Rai / Binet)
- Assessment of lymphocyte doubling time
- Assessment of organ function (creatinine clearance, cardiac function) if clinical or biochemical suspicion of significant abnormalities that may influence choice of treatment (eg use of fludarabine in patients with renal impairment).
- Additional prognostic tests (see section 3 below)

The following areas are those in which changes to current practice are anticipated and likely to influence current clinical practice

1.1 Immunophenotype

The current panel of 5 antibodies (CD5, CD23, FMC7, surface immunoglobulin and CD22/CD79b) recommended by the BCSH will continue to be used. However, the increasing use of Rituximab means that CD20 expression (expected to be low) is also increasingly likely to be measured.

1.2 Bone marrow or lymph node biopsy

This is no longer recommended at diagnosis in asymptomatic patients in whom the diagnosis has been established by examination of peripheral blood. This should however

be taken prior to initiation of treatment, in cases of unexplained cytopenias and for response assessment. A lymph node biopsy is not required routinely unless there is diagnostic uncertainty or there are concerns about high grade transformation.

1.3 CT scanning

This is not generally recommended in routine practice except where this may be useful to guide treatment (eg to exclude bulky disease - greater than 5cm short axis diameter) in cases where treatment using Alemtuzumab (Campath) is being considered), and to assess response in patients with previous bulky disease. The requirement for regular CT scanning may be more for patients in clinical trials due to US regulatory requirements (3 monthly imaging is currently required for patients in CLL trials regulated by the FDA).

1.4 Serum markers

A number of serum factors have been identified with prognostic significance in CLL including LDH, B_2-microglobulin (B2M), soluble CD23 and thymidine kinase, amongst which, elevated B_2M (>4 mg/l) appears to correlate most reproducibly with outcome (both response to treatment and survival). However, it is as yet it is unclear how this should be incorporated into routine clinical practice and routine measurement is not currently recommended.

1.5 Assessment of co-morbidities

Individualised therapy using treatment adapted to the patient's performance status and co-morbidities is being increasingly adopted in the treatment of CLL, allowing older (but medically fit) patients access to more effective therapy and to clinical trials. Formal assessment using comorbidity scales (eg the Charlson Index) is impractical for routine practice but may be required for entry into clinical trials.

1.6 Viral screening

The use of increasingly immunosuppressive therapies has been associated with an increased incidence of viral reactivation – CMV following Alemtuzumab and HBV/HCV following fludarabine (see section 5.2.3).

- CMV serology (IgG and IgM) is mandatory in all patients prior to treatment with Alemtuzumab. Patients at risk of viral reactivation (IgG positive) should also have weekly CMV PCR testing during and after treatment until recovery of immune function (CD4 count > $0.2x10^9$/l)
- HBV and HCV serological testing should be considered (although not currently mandatory) in all patients prior to fludarabine based chemotherapy with viral surveillance (PCR) undertaken in patients at risk of reactivation.
- HIV testing should be performed in patients considered at high risk of infection

2.0 The use of newer prognostic markers

The last decade has been marked by identification of a considerable number of biomarkers with prognostic significance in CLL. However, whilst these provide prognostic information, few are useful in guiding treatment decisions in individual patients and it remains unclear how these should be used in routine clinical practice. Furthermore, the cost, availability and lack of methodological standardization of some of the newer tests hinder their widespread use. It is anticipated that guidance for the use of prognostic tests in CLL will be contained within updated guidelines from the NCI and BCSH which should be referred to when published

2.1 Fluorescent in-situ hybridisation (FISH)

Genomic aberrations as determined by FISH can be detected on over 80% of patients with CLL. They have a skewed distribution, with mutations conferring an unfavourable prognosis being more common in patients with advanced disease and other poor prognostic factors.

2.1.1 *FISH – 17p*

17p deletions are uncommon in newly diagnosed patients (<5%) although are observed in up to 30-40% of patients with relapsed or refractory disease. Patients with 17p- have a very poor prognosis with a median survival of around 3 years. With the possible exception of allogeneic transplantation there is no evidence that early identification and treatment in early stage patients can overcome this adverse risk.

Part of the poor prognosis stems from the resistance to conventional chemotherapy conferred by inactivation of p53. The outcome (response rate and PFS) using fludarabine based chemotherapy (F, FC or FC-R) is poor, however there is emerging evidence that treatment with therapies other than conventional cytotoxics may be effective in this patient group (eg high dose steroids, Alemtuzumab and allogeneic transplantation). The use of alternative treatment modalities is being investigated in ongoing clinical trials.

2.1.2 *FISH – 11q, 12, 13q*

Each has been shown to have prognostic significance. Deletion of the 11q results in a poor prognosis with median overall survival (7 years vs 10 years with no mutations). Trisomy 12 is typically associated with relatively rapidly progressive disease although this does not appear to have a significant impact on overall survival, whereas deletions of 13q confer a favorable prognosis (median survival 11-12 years). Some, but not all studies have described an association between 11q deletions and resistance to chemotherapy (not significant in LRF-CLL4), however as with 17p- there is no evidence that early intervention and treatment of patients with stage A disease alters their overall outcome. Data from recent phase III studies comparing FC and FC-R in patients with CLL (REACH and GCLLSG CLL8) that the adverse prognostic impact of 11q deletions is abrogated in patients offered Rituximab in combination with FC chemotherapy.

2.1.3 *Conclusion*

Cytogenetic analysis by FISH (17p and 11q) gives useful prognostic information and may inform treatment decisions.

Outside the context of a trial, it is only currently recommended that this is performed at the point where treatment is required and where the result would influence treatment (eg patient eligible for Alemtuzumab, investigational treatment or allogeneic transplantation):

- **Newly diagnosed** patients who may be suitable for front line Alemtuzumab, investigational therapy or allogeneic transplant; predominantly under 60 years although consider in older patients with no co-morbidity.

- **Relapsed** / **refractory** patients of any age and potentially eligible for Alemtuzumab or investigational therapy.

Testing of patients with asymptomatic / stage A disease is not generally recommended and should only be undertaken if considering entry into a trial or if requested by the patient.

2.1.4 *Sample requirement*

5ml of peripheral blood or 2-5ml of bone marrow (in Lithium Heparin or cytogenetic culture medium + preservative free heparin) sent to

Cytogenetics Laboratory
Christie Foundation Trust
Wilmslow Road
Manchester
M20 4BX
Tel: 0161 446 3165

2.2 Other tests (V_H gene rearrangement, CD38, ZAP-70)

2.2.1 *V_H gene mutation*

Patients with an unmutated immunoglobulin heavy chain (V_H) locus (>98% homology to germline) have a worse prognosis than those with mutated genes (overall survival of around 10 years vs 20 years or more). In addition, the rearrangement of specific variable-region gene loci (eg $V_{H3\text{-}21}$) is associated with an unfavorable clinical outcome irrespective of the V_H mutation status. V_H sequencing is however not routinely available and does not influence the response to treatment.

2.2.2 *CD38 & ZAP-70*

Elevated expression of CD38 by CLL cells and aberrant expression of ZAP-70 are associated with a reduced overall survival and time to treatment in asymptomatic patients. CD38 expression is more common in patients with germline V_H genes although each factor has independent prognostic significance. Elevated ZAP-70 expression may be used as a surrogate marker for unmutated V_H gene status although the concordance between the tests is variable. Moreover, CD38 expression (analysed by flow cytometry)

varies with time and there is a lack of consensus concerning the level of expression that is significant, with cut-offs between 5% and 30% proposed. ZAP-70 expression is stable over the course of the disease although the optimal testing methodology (flow cytometry, immunohistochemistry, RT-PCR, or western blotting), and threshold to separate positive and negative results have not been determined. In addition to methodological problems, neither test predicts outcome following fludarabine based chemotherapy in newly diagnosed patients.

2.2.3 *Conclusion*

Routine analysis of CD38 and ZAP-70 expression or V_H gene mutational status is not currently recommended outside the context of a clinical trial.

3.0 Indications for treatment

The indications for treatment are as outlined in the BCSH guidelines (progressive Binet stage A, B, C disease):

- Progressive anaemia or thrombocytopenia (although see section 4.2)
- Bulky (>5cm) or progressive lymphadenopathy
- Massive (>6cm) or painful splenomegaly
- Lymphocyte doubling time < 6 months or 50% increase in < 2 months
- Constitutional symptoms directly attributable to disease (fever > 38℃, weight loss > 10%, severe fatigue, night sweats).

3.1 Patients with adverse prognostic factors

Outside the context of a clinical trial, treatment should only be initiated on the basis of standard indications (section 4.0), irrespective of the presence of factors associated with poor prognosis. Early intervention in patients with stage A disease associated with adverse risk factors using conventional chemotherapy does not lead to improved outcome and is not recommended. The use of newer therapies in this context (eg Lenalidomide or immunochemotherapy) is currently being investigated as part of a number of Clinical Trials. For further information contact Dr Adrian Bloor at the Christie Hospital.

3.2 Patients with autoimmune cytopenias

Autoimmune cytopenias occur not infrequently in patients with CLL (AIHA 10-25%; ITP 1-5%; PRCA 1%) either as a consequence of the underlying disease or treatment. The pathogenesis of these disorders is incompletely understood, however they are not typically the result of autoreactive monoclonal antibodies produced from the neoplastic clone and their occurrence does not necessarily signify disease progression. In the absence of overt evidence of disease activity, patients with autoimmune cytopenias should be treated initially with immunosuppressive therapy (primarily corticosteroids), with chemotherapy reserved for refractory cases (see review article section 7.3 and BSCH / NCCN guidelines. Although AIHA is a well described side effect of both chlorambucil and fludarabine, emerging data suggests that both agents may be used safely in patients with prior autoimmune haemolysis unless this was clearly a complication of previous treatment.

AIHA has also been described following FC-R immunochemotherapy. The MD Anderson reported an incidence of 6.5% in their series, in which most patients had a negative direct antiglobulin test (DAT).

4.0 Patient selection – assessment of age and comorbidities

Recent advances in treatment of CLL have led to the more widespread use of more aggressive treatment protocols. Although this has resulted in significant improvements in efficacy, this mandates a careful assessment of the risk:benefit of combination immunochemotherapy especially in elderly patients.

4.1 Age, demographics and co-morbidities

The majority of patients with CLL are diagnosed in their 7^{th} or 8^{th} decade (median age at diagnosis 72 years) and many will have impaired performance status (PS) or multiple co-morbidities (CM). Advancing age, impaired PS and presence of co-morbidities are all associated with a worse outcome and increased toxicity following chemotherapy although the correlation between each factor (age, PS, CM) is poor and many of the tools to formally assess co-morbidites are too cumbersome for routine clinical use. Combination immunochemotherapy (eg FC-R) should be used with caution in patients over 70 after a careful assessment of the risk:benefit and is not recommended in patients with poor PS or significant co-morbidities.

The German CLL study group has proposed a classification of CLL patients into three groups.

- ***Go-Go***. Patients (typically younger) without significant co-morbidities or impaired performance status fit for intensive chemotherapy
- ***Slow-Go***. Patients not fit for intensive treatment due to advanced age, poor performance status or co-morbidities.
- ***No-Go***. Patients fit for palliative treatment only.

4.2 Renal function

Fludarabine is contraindicated in patients with creatinine clearance < 30ml/min. A 50% dose reduction should be given for those with creatinine clearance 30-60 ml/min.

4.3 Autoimmune Haemolytic Anaemia (AIHA)

Fludarabine may be used in patients with a postive DAT or history of AIHA unless this is a side effect complicating prior use of the drug (see also section 3.2). Such patients must however be monitored closely for any evidence of haemolysis.

5.0 First line therapy – Clinical Trial

Where possible patients with newly diagnosed disease should be enrolled into a clinical trial.

5.1 Current clinical trials

Treatment should be delivered in a unit at appropriate BCSH level to deliver the therapy and supportive care. An extensive portfolio of commercial and non-commercial trials is available for patients with both newly diagnosed and relapsed disease. Further information may be obtained from

5.1.1 *Clinical Trials Research Unit (CTRU) – Leeds*

Maintains a database of NCRN adopted portfolio studies available in the UK
http://ctru.leeds.ac.uk/index

5.1.2 *Christie Hospital*

Contact Dr Adrian Bloor
http://www.christie.nhs.uk/research/themes/dg/htu/default.aspx

5.1.3 *Manchester Royal Infirmary*
Contact Professor John Yin

6.0 First Line therapy – Go Go

A suggested treatment algorithm for patients not enrolled in a clinical trial is shown in appendix 1. See also the guidance regarding supportive care (section 10.5)

6.1 Fludarabine, Cyclophosphamide and Rituximab (FC-R)

FC-R chemotherapy is not recommended in patients known to have 17p deletions or functional inactivation of p53 (see section 2.1.1). For all other patients with good performance status, FC-R is the standard first line treatment based on the superiority over FC (response and survival) demonstrated in the German CLL8 trial (see also NICE TA 174 http://www.nice.org.uk/nicemedia/live/11907/44906/44906.pdf).

Caution should be exercised using FC-R in elderly (>70) patients (see section 4.1). In contrast to the demographics of CLL (median age at diagnosis of 72), only 10% of the patients in the pivotal CLL8 trial were over 70; all had a good performance status (Cumulative Illness Rating Score < 6) and well preserved renal function (creatinine clearance > 60ml/min).

Cytoreduction with corticosteroids (eg prednisolone 1mg/kg for 21 days then tailed off over a further 7 days) prior to the introduction of cytotoxic chemotherapy may be considered as initial therapy in patients presenting with significant bone marrow suppression due to high levels if disease infiltration although is often relatively ineffective. Data from the LRF CLL-4 trial suggest that oral fludarabine is equally effective as the intravenous preparation when given at bioequivalent doses.

For supportive care see sections 10.5.1 and 10.5.2

6.1.4 *FC-R (oral)*

Fludarabine 24mg/m^2 d1-5 po
Cyclophosphamide 150mg/m^2 d1-5 po
Rituximab 375mg/m^2 for course 1 and then 500mg/m^2 for subsequent cycles.
Repeated on a 28 day cycle to maximum response (up to 6 cycles). Subsequent cycles may be delayed by 1-2 weeks in patients to allow haemopoietic recovery. In those with persistent cytopenias (neutrophils < $1x10^9$/l or platelets < $75x10^9$/l) after a previous treatment cycle, a 50% dose reduction should be considered.

6.1.5 *FC-R (iv)*
Fludarabine 25mg/m^2 d1-3 iv
Cyclophosphamide 250mg/m^2 d1-3 iv
Rituxumab 375mg/m^2 for course 1 and then 500mg/m^2 for subsequent cycles.
Cycle and dose reduction as above (section 6.1.4), mainly recommended for patients intolerant of oral treatment.

6.1.6 *Rituximab administration*
Significant infusion reactions (predominantly after the first infusion) occur more commonly in patients with CLL compared to NHL due to the circulating disease burden. Accelerated administration schedules are **not** recommended. For patients with a white count > $25x10^9$/l or bulky disease (spleen > 15cm, nodes > 5cm) the following is suggested:

- Steroid premedication prior to the first dose of Rituximab (60-100mg of prednisolone/methylprednisolone). Steroids may also be considered prior to subsequent doses although are not usually required.
- Splitting the first dose of Rituximab (100mg on day 1 and the remainder on day 2)
- Omission of Rituximab from the first cycle of treatment is **not** recommended. Co-administration of Rituximab with chemotherapy is recommended where possible to maximize the potential synergy between the agents.

6.2 Bendamustine
Patients with good performance status who are ineligible for Fludarabine based chemotherapy (eg due to impaired renal function, or previous Fludarabine induced haemolysis) should be offered treatment using Bendamustine (see also NICE TA 216

http://www.nice.org.uk/nicemedia/live/13343/53180/53180.pdf) on the basis of a randomized phase III trial that reported significantly higher response rates and response durations following treatment with Bendmustine compared to chlorambucil.

Bendumustine can be used safely in patients with significant renal failure (including those receiving haemodialysis) and in patients with previous autoimmune haemolysis. The available indicate that the toxicity of Bendamustine for treating CLL is less than that observed following FC although the results of studies directly comparing Bendamustine and Fludarabine based chemotherapy are awaited to confirm this.

6.2.1 *Recommended dosing – first line therapy*

Bendamustine 100mg/m^2 d1-2 iv

Repeated on a 28 day cycle to maximum response (up to 6 cycles). Subsequent cycles may be delayed by 1-2 weeks in patients to allow haemopoietic recovery. In those with persistent cytopenias (neutrophils < $1x10^9$/l or platelets < $75x10^9$/l) after a previous treatment cycle, a 30-50% dose reduction should be considered.

6.2.2 *Bendamustine+Rituximab*

There is little published data available concerning the use of Bendamustine and Rituxumab (B-R). Preliminary data from the German CLL-2M trial (a single arm phase phase II study investigating the use of B-R for first line therapy) did not suggest improved response rates compared to Bendamustine monotherapy and a larger phase III study comparing B-R with FC-R (German CLL-10 trial) is ongoing. Current NICE guidance does not recommend the use of Rituximab in combination with chemotherapy regimens other than FC. The use of B-R combination therapy is therefore not currently recommended outside of a clinical trial.

6.3 Conclusion

FC-R chemotherapy is recommended as first line treatment for patients with good performance status (ECOG <2) and acceptable renal function (GFR>30 ml/min). Dose reduction is essential is patients with GFR 30-60 ml/min. This may be used in patients over 70 years although careful patient selection is necessary in older patients. Bendamustine monotherapy is recommended for patients who are ineligible to receive FC-R

7.0 First Line therapy – Slow Go

There is little consensus regarding the optimal first line treatment of patients in whom FC chemotherapy is contraindicated due to age, performance status or renal function. Outside of a clinical trial, treatment options include chlorambucil (+/- steroids), reduced dose FC ('FC-lite'), and combination chemotherapy.

7.1 Chlorambucil

Currently this is the most widely used first line treatment for patients ineligible for fludarabine based chemotherapy.

Data from the LRF CLL-4 trial suggest that higher response rates (CR+nPR >20% vs <10%) may be achieved using a more dose dense regimen. Dose reduction is required for severe renal impairment or if the patient develops grade III-IV haematological toxicity. The CLL2 trial indicated no benefit for the addition of steroids and routine use of steroids is not recommended.

7.1.3 *Chlorambucil treatment regimen*

The suggested regimen is 10mg/m^2 po d1-7 every 28 days for 6-12 cycles as per the LRF CLL-4 trial. The number of cycles is dependent on response and toxicity. Patients should be treated to maximal response; treatment beyond 6 cycles may be considered in patients who have not achieved a CR at this point but show ongoing evidence of response. Dose reduction can be considered in patients who develop significant bone marrow toxicity.

7.2 Bendamustine

Bendamustine offers significantly greater efficacy than Chlorambucil for first line treatment of CLL (PFS 21.6 months vs 8 months) although at the cost of greater toxicity (grade 3-4 toxicity 40% vs 19%) and requirement for intravenous administration. This is NICE approved for first line therapy in patients who are ineligible for Fludarabine based chemotherapy (eg due to age or comorbidities).

See also NICE TA216 http://www.nice.org.uk/nicemedia/live/13343/53180/53180.pdf. Bendamustine should therefore be considered as an alternative to chlorambucil in this patient population.

7.2.4 *Bendamustine treatment regimen*

See section 6.2.1. A reduced dose of 70mg/m^2 should be considered in patients who have significant bone marrow suppression at diagnosis or following initiation of treatment.

7.3 Front line treatment with fludarabine

The response rate using single agent fludarabine as first line treatment is higher than that achieved using chlorambucil, however the results of the LRF CLL4 trial indicate that this does not translate into improved survival. Fludarabine monotherapy was not recommended as initial treatment for patients with CLL in a NICE technology appraisal published in 2007 (http://guidance.nice.org.uk/TA119/guidance/pdf/English). A significant proportion of patients will respond to fludarabine having failed prior chlorambucil and its use is primarily recommended in this context.

7.4 'FC(-R)-Lite'

A number of regimens have been described for use in elderly or unfit patients with CLL or indolent non-Hodgkin's lymphoma. These may be are associated with less toxicity (especially haematological) than the full dose regimen although the efficacy of dose reduced treatment is uncertain. A suggested regimen is as below:

Fludarabine 25mg/m^2 (maximum 40mg) po d1-4
Cyclophosphamide 120mg/m^2 po d1-4
Cycle repeated every 28 days or following haematological recovery (see section 6.1.4)

For supportive care guidelines see section 10.5.2

7.5 Combination chemotherapy

Although CVP or COP may be considered for patients unfit for FC chemotherapy there is no evidence that there is any superiority of combination treatment (with or without

anthracyclines) over chlorambucil monotherapy (eg MRC CLL1 and CLL3 trial). CVP type regimens are therefore **not** recommended.

7.6 Rituxumab in combination with non-FC chemotherapy

A benefit for the addition of Rituximab to non-FC chemotherapy may be inferred from the recent FC vs FC-R phase III studies, although there are no data to confirm this. Preminary data from trials combining Rituxumab with other chemotherapy regimens (eg Chlorambucil and Bendamustine) suggest that the benefit for the addition of Rituxumab is modest. Until there are more data available to demonstrate the superiority of the addition of Ritxumab to other regimens, or NICE support the broad use of R-chemotherapy for first line therapy, the addition of Rituximab to non-FC regimens is not recommended.

7.7 Conclusions

Chlorambucil remains the most widespread treatment for this patient population. Bendamustine is more effective and should be considered; although this is associated with greater toxicities these are typically manageable. Rituximab is only recommened in combination with FC although fludarabine based regimens are generally not recommended in this patient population due to the toxicity.

8.0 First Line therapy – No Go

Treatment for patients with severe comorbidities or extreme age should be considered on a case by case basis. Options include low dose steroids, chlorambucil or radiotherapy and supportive care.

9.0 First line treatment of patients with chromosome 17p deletions

17p deletions are uncommon in patients with newly diagnosed disease (5-7% of patients), however in cases known carry a deletion, fludarabine based chemotherapy is not recommended as this unlikely to be effective (median survival less than 1 year) and may reduce the efficacy of subsequent treatments.

Currently however there is no standard therapy for front line treatment in this group and enrollment into a clinical trial is recommended where possible (see section 5.0). Outside of a trial, treatment options are Alemtuzumab (non bulky disease) or high dose steroids.

9.1 Alemtuzumab

Alemtuzumab is the most effective agent for treating this patient population although the efficacy is reduced in patients with bulky disease. It is suggested that Alemtuzumab is administered subcutaneously rather than intravenously (30mg 3 times per week for 12 weeks after an initial test doses of 3mg and 10mg) to reduce the treatment related toxicity.

For supportive care guidelines see section 10.5.4

9.2 High dose steroids

Methylprednisolone (1g/m^2 for 5 days repeated monthly for up to 4-6 cycles) is effective for treating patients with CLL and associated p53 deletion although is often associated with significant toxicity (metabolic and infectious). Pulsed dexamethasone (40mg for 4 days every 2-4 weeks) may be considered as an alternative and is typically better tolerated. In patients with bulky disease a steroid pre-phase may be considered prior to Alemtuzumab.

9.3 Combination therapy

The use of combination therapy with high dose steroids and Alemtuzumab has been investigated in clinical trials in the UK and Germany. Preliminary data from the UK CLL-206 study indicate that this is more effective than monotherapy although associated with greater toxicity.

9.4 Conclusions

Outside of a trial, patients with non bulky disease should be offered treatment with Alemtuzumab. High dose steroids are suggested for patients with bulky disease, in whom the response may be consolidated with Alemtuzumab. Combination therapy is only recommended in the context of a clinical trial.

10.0 Other drugs – Alemtuzumab, Mitoxantrone and Pentostatin

10.1 Alemtuzumab

Outside the context of patients with p53 deletions, Alemtuzumab has been investigated for first line therapy in a phase III trial (CAM307) in comparison to chlorambucil. Alemtuzumab is more effective that chlorambucil although the response rate/response duration are significantly less than those reported with FC-R or Bendamustine.

Alemtuzumab has also been investigated in a number of trials for eradiation of minimal residual disease (MRD) following chemotherapy although a number of the studies were closed due to unacceptable toxicity.

10.2 Mitoxantrone

Two phase II trials from Barcelona and the MD Anderson have reported impressive response rates using Fludarabine, Cyclophosphamide and Mitoxantrone (FCM) as first line CLL treatment A small Spanish single arm phase II study reported that the response to FC chemotherapy is improved with the addition of mitoxantrone (FCM). The benefits of adding mitoxantrone to FC-R is being investigated as part of an NCRN phase II trial (ADMIRE)

10.3 Pentostatin

Trials from the US and Europe have both demonstrated that pentostatin (alone or in combination with alkylating agents and rituximab) is effective in the treatment of CLL although currently there is no evidence to suggest that pentostatin containing regimens are more effective or better tolerated than those containing fludarabine.

10.4 Conclusion

As first line therapy, Alemtuzumab should be restricted to patients 17p deletion. Treatment aimed at MRD eradication is only recommended as part of a clinical trial. None of the other agents are currently recommended for routine use.

10.5 Supportive care

10.5.1 *For all patients*

- Allopurinol (100-300 mg od po, dose adjusted to renal function) is recommended during the first cycle of treatment.

- Local policies for management of febrile neutropenia should be followed.
- Prophylactic antibiotics (other than detailed below) or the routine use of immunoglobulin replacement are not in general recommended (see 2003 BCSH guidelines for more details)

10.5.2 *For patients treated with fludarabine containing regimens*

- Co-trimoxazole 480-960mg mon/wed/fri or in accordance with local policy. Dapsone 100mg od, or nebulised pentamidine 300mg monthly are alternatives if allergic/intolerant. Treatment should be continued for 6 months following cessation of treatment or until the peripheral blood CD4 count is $>0.2x10^9/l$
- Aciclovir 400mg bd is recommended, particularly for patients treated with fludarabine containing combination chemotherapy, continued for 6 months following cessation of treatment
- Hepatitis B/C surveillance using PCR should be performed in patients at risk of viral reactivation (see section 1.6). Liaison with a Hepatologist for advice with regard to management is recommended in these patients prior to initiation of treatment.
- G-CSF should be considered in patients with persistent treatment related neutropenia ($< 0.5x10^9/l$) not responsive to dose reduction, especially in those over 70 in whom serious infections may occur more frequently.
- Blood products should be irradiated.
- Oral FC is moderately emetogenic and patients should receive antiemetics in accordance with local policy.

10.5.3 *For patients treated with Rituximab containing regimens*

Additional precautions are suggested for administration to minimize the risk of infusion related toxicity (see section 6.1.6)

10.5.4 *For patients treated with Alemtuzumab containing regimens*

- Co-trimoxazole and aciclovir prophylaxis (dose as for fludarabine) continued until immune reconstitution (peripheral blood CD4 count $> 0.2x10^9/l$), which may take several months.
- Patients at risk of hepatitis should be managed as for fludarabine (above)

- **CMV screening prior to treatment is mandatory**. All patients at risk of CMV reactivation (CMV IgM positive) must have weekly surveillance (whole blood PCR) during treatment and continuing until immune reconstitution (peripheral blood CD4 count > $0.2x10^9$/l). Treatment should be initiated in patients with asymptomatic viral reactivation (2 positive tests or a single positive test above log 3) and continued until 2 sequential tests at or below the limit of quantification. The local policy for treatment of CMV reactivation should be followed and liaison with a Virologist is recommended of advice is required.
- G-CSF should be administered to patients with treatment related neutropenia (< $0.5x10^9$/l), platelets should be given in accordance with national guidelines (transfuse if count < $10x10^9$/l or < $20x10^9$/l if febrile / haemorrhagic).
- Blood products should be irradiated.

11.0 Treatment of relapsed disease

There is no standard treatment for patients with relapsed disease particularly following initial therapy with FC (or similar). Choice of therapy depends on several factors including first line treatment regimen, age & performance status and the duration of the first remission. A suggested algorithm is shown in appendix 1.

As for primary therapy, recruitment into a clinical trial should be considered where possible. A number of agents are being investigated in the context of relapsed disease (eg 2^{nd}/3^{rd} generation anti-CD20 antibodies, B-cell receptor signaling pathway inhibitors, anti-apoptosis inhibitors, Lenalidomide).

11.1 Lenalidomide

Two phase II trials reported encouraging response rates of up to 47% in patients with refractory disease. This is currently being investigated as part of further studies (contact Dr Adrian Bloor at the Christie Hospital). Use outside of a trial is not generally recommended.

11.2 Ofatumumab

A number of studies have investigated the use of this second generation fully human anti-CD20 antibody in CLL as either monotherapy or in combination with chemotherapy.

This is currently licensed for treatment of patients who are refractory to both Fludarabine and Alemtuzumab on the basis of a phase II trial demonstrating response rates of up to 50% in this patient population.Ofatumumab is currently only routinely recommended for this indication; use for other indications should be restricted to a clinical trial.

12.0 Stem cell transplantation

12.1 Autologous Stem Cell Transplantation

A high incidence of myelodysplasia / AML (>10%) has recently been reported amongst patients enrolled in the MRC-CLL5 pilot study of autologous transplantation (ASCT), leading to early closure of the main trial in 2007. Several explanations for this are possible including the use of total body irradiation for transplant conditioning and prior fludarabine chemotherapy, and ASCT is not currently recommended in this disease group.

12.2 Allogeneic Stem Cell Transplantation

The role of allogeneic transplantation (alloSCT) has not yet been conclusively established in CLL. However, there are emerging data that alloSCT conditioning with reduced intensity conditioning is effective, can overcome adverse risk factors (inclusing deletions of 17p) with the potential for long term disease free survival, eradication of minimal residual disease, acceptable toxicity and is deliverable to patients into their mid to late 60's. It is recommended that alloSCT is considered in the following groups:

- Patients < 65, ECOG performance status ≤ 1

  AND
- Patients refractory to fludarabine monotherapy - response < 6 months (CR/PR ≥ 2)
- Patients with short remission duration (< 12 months) following purine analogue based combination therapy treatment (CR/PR ≥ 2)
- 17p deletions (CR1)
- PLL (CR1). See section 14.0

  Contact: Dr Adrian Bloor (Christie Hospital)

  Professor John Yin (Manchester Royal Infirmary)

13.0 Goal of therapy and assessment of response

The quality of remission obtained following chemotherapy has been consistently associated with improved time to progression in patients with CLL, although using conventional treatments (eg chlorambucil or fludarabine) and response criteria (eg FBC, and bone marrow cytology) this does not translate into improvements in overall survival. However, using newer treatments (eg FC-R, FCM and Alemtuzumab) it is possible to achieve MRD negative remissions which may confer a survival advantage, although longer follow up of ongoing trials will be needed to confirm this.

13.1 Response criteria (from 2008 IwCLL guidelines)

Current response criteria are shown in Appendix 2 derived from the recently updated IwCLL guidelines. These should be followed for patients in clinical trials and **may** be applicable in routine practice.

13.2 Complete remission

With increasingly effective treatment for patients with newly diagnosed disease, complete remission is increasingly being used as an endpoint for CLL trials. It is likely that the definition of CR will change in the updated NCI guidelines. In particular this is likely to include assessment of MRD (see below) and allow CR in the presence of ongoing cytopenias (as often happens in patients receiving Alemtuzumab maintenance).

13.3 MRD monitoring

Several questions remain unanswered:

- Guidelines for MRD monitoring using 4-colour flow cytometry have recently been published and should reduce inter-laboratory variation due to standardization of methodology
- The optimal treatment that should be employed to achieve MRD eradication (aggressive front line therapy vs post treatment consolidation)
- Patient selection – potential benefit of achieving MRD –ve remission may be offset by increased toxicity from use of more intensive treatment.
- MRD-ve remission may be achieved following treatment with Alemtuzumab and FC-R. MRD monitoring may be considered in selected patients in the event that

this will guide further therapy (eg extended Alemtuzumab therapy or entry into a clinical trial of MRD eradication maintenance therapy – see section 5.1)

13.4 Conclusion

Although it has not yet been shown to translate into an overall survival advantage, achievement of complete remission is likely to be increasingly adopted as the goal of treatment, especially in clinical trials, with MRD monitoring likely to be increasingly applied especially in younger patients. In routine practice, it is however still recommended that standard response criteria (see the BCSH and IwCLL guidelines) are applied and MRD monitoring is generally only used in the context of a trial. For further advice contact Dr Adrian Bloor at the Christie Hospital.

14.0 Prolymphocytic Leukaemia

Prolymphocytic leukaemias are very uncommon and although they were previously considered variants of CLL, it is clear from gene expression profiling that these are biologically distinct diseases. The prognosis is poor and the rarity of the disorders has hampered the development of clinical trials to improve treatment outcome.

A number of new agents (eg PARP inhibitors) are being investigated for treatment of PLL as part of clinical trials and these should be considered wherever possible. For further information contact Dr Adrian Bloor – Christie Hospital.

14.1 B-prolymphocytic leukaemia

14.1.1 *Demographics, presentation and immunophenotype*

Typically presents in patients in their 7th decade with a rapidly rising white count, usually >100x10^{9}/l at presentation. By definition, prolymphocytes account for > 55% of the circulating lymphoid cells. The immunophenotype is distinct from CLL (CLL score normally 0-1). The leukaemic cells typically demonstrate strong expression of B cell antigens (CD19, CD20, CD79a/b, CD22, FMC7) and immunoglobulin, whilst CD5 and CD23 are only expressed in the minority of cases. *P53* dysregulation is common (50% of cases have del17p) accounting in part for the observed resistance to treatment.

14.1.2 *Prognosis*

The prognosis is uniformly poor with a median survival of 30-50 months.

14.1.3 *Treatment*

There are no ongoing trials for patients with B-PLL and the the published literature regarding treatment is small. Alkylator therapy (eg chlorambucil) is typically ineffective, although a proportion of patients respond to combination chemotherapy such as CHOP. To date, the best results described have been obtained using purine analogue based therapy (fludarabine, cladribine or pentostatin) with reported response rates of up to 50%. Whether the outcome of treatment can be improved by using combination purine analogue based chemotherapy (eg FC) or using monoclonal antibodies (Rituximab or Alemtuzumab) is uncertain.

Younger and fitter patients may be considered for stem cell transplantation in first remission. Splenectomy or splenic irradiation can be considered in patients with massive splenomegaly.

14.1.4 *Conclusion – chemotherapy*

Treatment of B-PLL remains suboptimal. First line treatment with Fludarabine or Cladribine is suggested for patients with acceptable renal function and performance status. The benefit from the addition of Rituxumab is unproven but this may be considered given the poor prognosis of the disease. Alemtuzumab or steroids are suggested for patients with relapsed disease

Patients with very impaired performance status should be offered supportive care.

14.2 T-prolymphocytic leukaemia

14.2.1 *Demographics, presentation and immunophenotype*

Patients typically present in their 7th decade with a high circulating white blood count, lymphadenopathy and hepatosplenomegally. Skin infiltration and effusions are relatively common. In most cases the prolymphocytes are medium sized with irregular nuclei and prominent nucleolus; in a minority of cases the cells resemble Sézary cells. The cells have a post thymic phenotype expressing CD2, CD3 and CD7 (strong) whilst CD1a and

TdT are negative. Two thirds of patients have a CD4+/CD8- phenotype, 20% are CD4+/CD8+ (a feature almost unique to T-PLL) and the remainder are CD4-/CD8-. Most cases exhibit strong expression of CD52. Chromosomal abnormalities of chromosome 14 leading to dysregulation of *TCL1* are seen in 80% of cases.

14.2.2 *Prognosis*

The disease is typically aggressive with median survival of less than 1 year. A more indolent course is initially observed in small proportion of patients although the disease course typically accelerates after 2-3 in this group of patients.

14.2.3 *Treatment*

Alkylating agents are typically ineffective. Response rates of 40-50% have been reported using purine analogues although the responses are typically short-lived. The best results reported have been obtained using Alemtuzumab with response rates of over 50% in relapsed patients and up to 100% in patients with newly diagnosed disease. Responses are however typically shortlived irrespective of the treatment used. Longer term remissions may be achieved using stem cell transplantation (autologous or allogeneic).

14.2.4 *Conclusions*

Alemtuzumab (30mg 3x weekly for 12 weeks) is recommended as first line treatment for patients with adequate performance status. Subcutaneous administration reduces the treatment related toxicity. Younger patients with good performance status who respond to treatment should be referred for stem cell transplantation. Re-treatment with Alemtuzumab may be considered in relapsed patients not suitable for transplantation if the duration of initial response was > 12 months.

Fludarabine, steroids or supportive care should be considered for patients unfit for Alemtuzumab.

15.0 Patient support

Patients should be given the opportunity to obtain information about CLL via written information, the internet and contact with patient support associations. The 2003 BSCH guidelines contain contact details for many of these. In addition, the CLL Support

Association has been founded since the guidelines were published and they may be contacted via their website http://www.cllsupport.org.uk/.

16.0 References

16.1 Published guidelines

BCSH guidelines (2003):

http://www.bcshguidelines.com/pdf/chronicLL_050504.pdf

NCCN guidelines – within guidelines for management of NHL (2009):

http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

IWCLL guidelines (2008):

Hallek M et al Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute Working Group 1996 guidelines. Blood 2008:111;5446-56

BSBMT guidelines for Stem Cell Transplantation (2010)

http://www.bsbmt.org/pages/64-Indications_Table

16.2 Treatment with FC-R

Keating MJ et al Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab as Initial Therapy for Chronic Lymphocytic Leukemia. J Clin Oncol 2005:23;4079-88

Wierda W et al Chemoimmunotherapy With Fludarabine, Cyclophosphamide, and Rituximab for Relapsed and Refractory Chronic Lymphocytic Leukemia. J Clin Oncol 2005:23;4070-8

Hallek M et al Addition of rituximab to fl udarabine and cyclophosphamide

in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164

Robak T et al Rituximab, Fludarabine, and Cyclophosphamide (R-FC) Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756

Foon KA et al Chemoimmunotherapy With Low-Dose Fludarabine and Cyclophosphamide and High Dose Rituximab in Previously Untreated Patients With Chronic Lymphocytic Leukemia. J Clin Oncol 2009:27;498-503

16.3 Treatment with other regimens

Knauf W et al Phase III Randomized Study of Bendamustine Compared with Chlorambucil in Previously Untreated Patients with Chronic Lymphocytic Leukemia. J Clin Oncol 2009;27:4738

Hillmen P et al Alemtuzumab Compared With Chlorambucil As First-Line Therapy for Chronic Lymphocytic Leukemia. J Clin Oncol 2007;27:5616

Wierda W et al Ofatumumab As Single-Agent CD20 Immunotherapy in Fludarabine-Refractory Chronic Lymphocytic Leukemia. J Clin Oncol 2010;28:1749

Chanan-Khan A et al Lenalidomide for the Treatment of B-Cell Malignancies. J Clin Oncol 2008;26:1544

16.4 Review articles

Hallek M et al State of the art treatment of chronic lymphocytic leukaemia. Blood Rev 2011;25:1

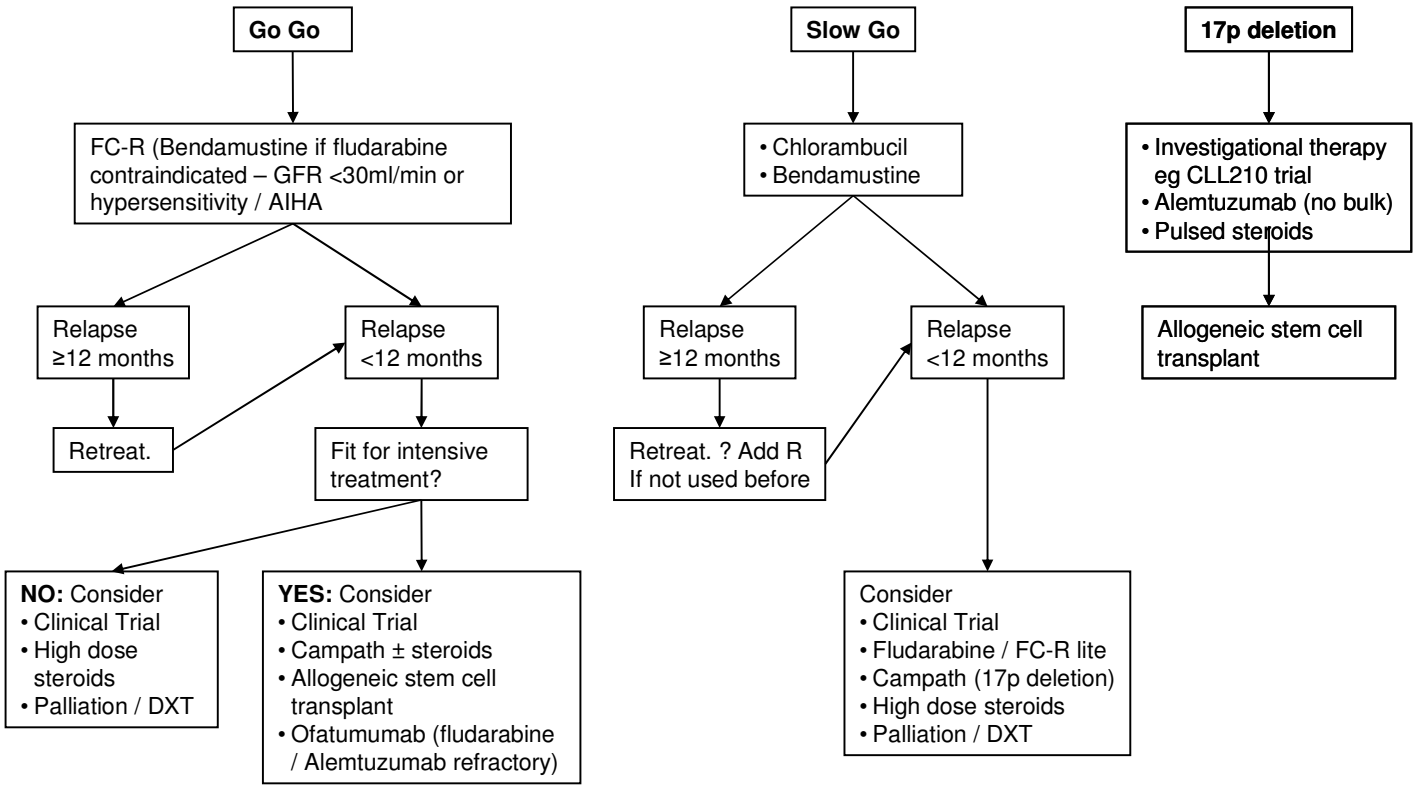
Dreger P et al Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia 2007:21;12-7

Hamblin TJ Autoimmune Complications of Chronic Lymphocytic Leukemia. Semin Oncol 2006:33;230-9

Dearden C Disease-specific complications of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2008:450

Dungarwalla M et al Prolymphocytic Leukaemia of B- and T-cell subtype: a state-of-the-art paper. Eur J Haematol 2008:80;469-76

17.0 Appendix 1 – Treatment algorithm for patients not in clinical trials



18.0 Appendix 2 – Response Criteria

Parameter	CR	PR	SD	PD
Group A				
Lymphadenopathy[1]	None > 1.5cm	Decrease ≥ 50%	Change < 50%	Increase ≥ 50%
Liver & Spleen	Normal size	Decrease ≥ 50%	Change < 50%	Increase ≥ 50%
Constitutional symptoms	None	Any	Any	Any
Peripheral blood neutrophil count	>1.5x10^9/l	<1.5x10^9/l or increase ≥ 50% over baseline	Any	Any
Circulating clonal B lymphocytes[2]	None	Decrease ≥ 50% over baseline	Change < 50%	Increase ≥ 50% over baseline
Group B				
Platelets	>100x10^9/l	>100x10^9/l or increase ≥ 50% over baseline	Change < 50%	Decrease ≥ 50%
Haemoglobin[3]	>11g/dl	>11g/dl or increase ≥ 50% over baseline	Increase < 50% over baseline or decrease < 2g/dl	Decrease ≥ 2g/dl
Bone Marrow Aspirate and Trephine Biopsy[4]	Normocellular, <30% lymphocytes. No B-lymphoid nodules	≥30% lymphocytes , or B-lymhoid nodules or not done	No change	Increase to ≥30% lymphocytes from normal

[1]Assessed at multiple lymph node sites

[2]Using conventional flow cytometry and does **not** require 4-colour methodology used for assessment of MRD

[3]Unsupported by transfusion or erythropoietin

[4]Hypocellular marrow but otherwise CR should be designated CRi

Complete Remission (CR): All criteria met (groups A and B) for ≥ 3 months

Partial Remission (PR): At least one from group A and one from group B for ≥ 2 months

Stable Disease (SD): At least one from group A **or** one from group B

Progressive Disease (PD): All criteria met (groups A and B)