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 – 2018)[1], European Society of Medical Oncology Clinical Practice Guidelines (ESMO – 2015, 2017)[2,3] and International Working Party on CLL (IwCLL – 2018)[4] guidelines.

1.0 Investigations at diagnosis and diagnostic criteria

Recommended baseline investigations at diagnosis are largely unchanged from previous guidelines:

- FBC, blood film and reticulocyte count
- Renal function, liver function, LDH, 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).
- HIV, HepB, HepC serology should be undertaken prior to treatment. CMV serology should also be checked prior to therapies leading to increased risk of viral reactivation (eg alemtuzumab, idelalisib)
- Additional prognostic tests (see section 3 below)

A diagnosis of CLL requires the presence of a peripheral blood lymphocytosis ($\geq 5x10^9$/l) with a characteristic phenotype present for at least 3 months. The presence of a persistent clonal lymphocytosis at a lower level in the absence of any other evidence of disease is defined as monoclonal B-cell lymphocytosis (MBL) although the majority of such cases do not progress to CLL. A proportion of patients have predominantly nodal disease without a significant lymphocytosis (defined as small lymphocytic lymphoma - SLL) requiring a tissue biopsy to establish the diagnosis

[1] Schuh A et al Br J Haematol 2018;182:344
[2] Eichhorst B et al Ann Oncol 2015;26s5:v78
[3] https://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations
[4] Hallek M et al Blood 2018;131:2745

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. An extended antibody panel may be utlilised in cases where there is diagnostic uncertainty.

1.2 Bone marrow or lymph node biopsy

Not routinely required although can be considered in cases of unexplained cytopenias and for response assessment. Bone marrow biopsies may be required for patients enrolled in clinical trials. A lymph node biopsy is not required routinely unless there is diagnostic uncertainty or there are concerns about high grade transformation.

1.3 Imaging

Published guidelines recommend a baseline chest x-ray prior to initiation of treatment however, CT scanning or ultrasound are not generally recommended in routine practice and results rarely inform decisions regarding treatment. Routine CT scans are generally required in clinical trials for baseline staging and detailed response assessment. CT-PET scanning should only be undertaken for assessment of patients with suspected or proven high grade (Richter) transformation.

1.4 Serum markers

A number of serum factors have been identified with prognostic significance in CLL including LDH, B_2-microglobulin (B2M) correlate most reproducibly with outcome (both response to treatment and survival) and baseline assessment can be considered.

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 Co-morbidity Index or Cumulative Illness Rating Scale - CIRS) may be considered. The CIRS score has been validated in

clinical trials and can be used for determining optimal treatment and for screening patients prior to entry into clinical trials.

2.0 Molecular genetics and other prognostic biomarkers

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, and those conferring an unfavourable prognosis are more common in patients with advanced disease and other poor prognostic factors. The results of FISH testing can be used at diagnosis in order to distinguish CLL from other lymphoproliferative disorders and also provides important information regarding prognosis and response to therapy. Testing can be considered at diagnosis and is recommended prior to initiation of any line of treatment.

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- requiring treatment have a poor prognosis using conventional chemotherapy although this can be partly overcome using newer treatments (eg B-cell receptor antagonists). Assessment of 17p deletional status should be undertaken prior to any line of therapy. The optimal cut-off for determining a positive FISH result is uncertain but currently a threshold of ≥10% is recommended to inform treatment decisions. Deletions 13q is the most common abnormality observed in CLL patients and associated with a favourable prognosis. Deletion of 11q or trisomy 12 have historically been associated with treatment resistance or a more aggressive disease course although this is largely overcome with newer treatment.

2.2 Conventional karyotyping

Recent data confirms previous observations showing that patients with complex karyotypes (≥ 3 abnormalities) have a worse prognosis that those without. It is however unclear how this should be incorporated into patient management and routine testing is not recommended.

2.3 Molecular genetics

Results from prospective trials (eg German CLL8)[5] have shown that p53 dysregulation has an equivalent impact on prognosis when assessed by either deletion (FISH) or mutation (sequencing). The majority of patients will demonstrate p53 dysregulation by both testing modalities although around 5% of patients with p53 mutation have no evidence of deletion.[6] As such mutational testing (Sanger sequencing or next generation sequencing) is recommended in all patients at initiation of each line of treatment. A number of other prognostically significant recurrent genetic mutations (eg NOTCH1, SF3B1, BIRC3) can be identified by sequencing although routine testing for these is not currently recommended.

2.4 Immunoglobulin heavy chain (IGVH) sequence

CLL patients may be dichotomized by the presence or absence (≥98% germline sequence) of somatic mutations in the IGVH gene. Mutated IGHV sequence is associated with a significantly better prognosis and response to conventional immunochemotherapy. Testing is now widely available and assessment of IGVH mutational status may be considered in patients requiring treatment.

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 (unless primarily due to autoimmune disease)
- 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°C, weight loss > 10%, severe fatigue, night sweats).

[5] Stilgenbauer S et al Blood 2014;123:3247
[6] Zenz T et al J Clin Oncol 2010;28;4473

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 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.

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 BCSH 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 7th or 8th 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 inferior outcomes 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-morbidities 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.

- Fit non co-morbid ('go-go') patients (typically younger) without significant co-morbidities or impaired performance status fit for intensive chemotherapy
- Co-morbid or elderly ('slow-go') patients not fit for intensive treatment due to advanced age, poor performance status or co-morbidities.
- Very unfit co-morbid patients ('no-go') suitable 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 positive 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

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Manchester Royal Infirmary – Dr Jane Norman (jane.norman@mft.nhs.uk)

6.0 First line therapy outside of trials

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 7.0)

6.1 Which patients should be treated with fludarabine cyclophosphamide and Rituximab (FCR)?

FCR remains the standard of care for first line therapy in fit non-comorbid patients without evidence of p53 dysregulation although this is likely to evolve based on the results of ongoing randomized phase III trials investigating the use of newer treatments (eg ibrutinib). Emerging data indicate that this can produce very durable remission in a subset of patients (IGVH mutated and achieving minimal residual disease negative complete remission)[7]

- 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 a minority of patients treated with FCR in clinical trials were over 70; all had a good performance status (Cumulative Illness Rating Score < 6) and well preserved renal function (creatinine clearance > 60ml/min).
- Based on the results of UK trials,[8] FCR can be used safely in patients with impaired renal function although fludarabine dose reduction is required for GFR < 60ml/min
- Significant infusion reactions (predominantly after the first infusion) occur more commonly in patients with CLL. For patients with a white count > 25x109/l or bulky disease (spleen > 15cm, nodes > 5cm) it is recommended that the first

[7] Thompson PA et al Blood 2016;127:303
[8] Munir T el at Leukemia 2017;31:2085

dose of rituximab is divided (100mg D1 and remainder D2). All patients should receive steroid pre-medication; methylprednisolone (100mg) appears to be more effective that hydrocortisone. 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

- For supportive care see sections 7.1 and 7.2

6.2 Which patients should receive first line therapy with Bendamustine and Rituximab?

Fit non-comorbid patients (go-go) who have no evidence of p53 dysregulation and are ineligible for fludarabine based chemotherapy (eg due to impaired renal function, or previous fludarabine induced haemolysis) may be considered for treatment with BR. This is an effective first line therapy which can safely be used in patients with significant renal failure (including those receiving haemodialysis) and in patients with previous autoimmune haemolysis. Results of the German CLL10 trial indicate that BR leads to fewer complications than FCR although this is offset by shorter progression free survival.[9]

BR is also a treatment option for some slow go patients who would otherwise be candidates for chlorambucil (CBL) based therapy. Results of the phase III MABLE trial (BR vs CBL-R) demonstrated that BR leads to a longer PFS compared to CBL-R with similar toxicity profile.[10]

6.3 What is the optimal first line treatment for patients with p53 dysregulation?

Results of treatment with (immuno)-chemotherapy are markedly worse for patients with p53 dysregulation than for those without. All patients being considered for treatment must have p53 status assessed before starting therapy by FISH and sequencing (see section 2.0). Outcomes using newer treatments (eg B-cell receptor antagonists – ibrutinib/idelalisib or BCL-2 inhibitors – venetoclax) are significant better than those

[9] Eichhorst B et al Lancet Oncol 2016;17:928
[10] Michallet A-S et al Haematologica 2018;103:698

previously reported using chemotherapy and are recommended for treating all patients with p53 dysregulation.

- **Ibrutinib:** Effective and generally well tolerated with longest available follow up. Characteristic lymphocytosis following initiation of treatment although this normally resolves by 9 months and is not of any prognostic significance. Complicated by arthralgia, skin rash, cytopenia, gastrointestinal disturbance. Easy bruising in up to two thirds of patients with more significant haemorrhagic complications in up to 5%; warfarin contraindicated. Up to 10% of patients develop atrial fibrillation with smaller incidence of more significant arrhythmias and sudden death; 20% of patients develop hypertension and cardiac assessment is recommended prior to treatment for patients with significant cardiac co-morbidity. May lead to opportunistic infections (eg fungal and pneumocystis jirovecii). Wide range of drug interactions and not recommended in patients with severe renal impairment.[11]
- **Idelalisib+rituximab:** Effective and often initially well tolerated although dose limiting toxicity is common (cytopenia, colitis, hepatitis, pneumonitis and opportunistic infections) especially as first line therapy. Characteristic lymphocytosis following initiation of treatment although this normally resolves by 9 months and is not of any prognostic significance. Fewer drug interactions that with ibrutinib and can be used with warfarin and in patients with renal failure.[12]
- **Venetoclax:** Effective although shorter follow up that for ibrutinib. Risk of tumour lysis syndrome requiring careful dose escalation during first 5 weeks of treatment. Neutropenia common although can normally be managed with GCSF. Multiple drug interactions and not recommended for patients with severe renal impairment.[13]

Due to the significant potential toxicities associated with idelalisib in untreated patients, this is rarely if ever indicated. Ibrutinib is recommended as first line therapy and venetoclax is an option if ibrutinib is contraindicated (eg due to need for warfarin, drug interactions, intolerance or cardiac disease). For practical considerations regarding use of ibrutinib see section 6.5.

[11] Gribben JG et al Br J Haematol 2018;180:666
[12] Lampson BL et al Blood 2015;126:497
[13] Davids MS et al Clin Cancer Res 2018;24:4371

6.4 What is the optimal antibody to combine with chlorambucil for co-morbid patients?

Results of two trials (COMPLEMENT-1 and German CLL-11) demonstrated that chlorambucil (CBL) combined with anti-CD20 antibodies is an effective and well tolerated treatment for front line treatment of co-morbid or elderly CLL patients.[14,15] Chlorambucil plus obinutuzumab (obin) led to higher response rate (ORR) and longer PFS compared to chlorambucil monotherapy. The use of both obinutuzumab and ofatumumab (ofa) in combination with chlorambucil led to improved ORR/PFS compared to chlorambucil and rituximab. The differences in patient population and chlorambucil dosing mean that it is not possible to formally compare the results of the trials and both CBL-ofa and CBL-obin may be considered for treatment in this patient population.

- The MRC CBL dosing schedule (10mg/m^2 D1-7) is suggested irrespective of the antibody employed
- Obinutuzumab is associated with higher rate of infusional toxicity that rituximab especially on dose 1 and 2. Methylprednisolone is required as premedication rather than hydrocortisone and the first dose should be given as a divided dose on D1 and D2

6.5 Use of ibrutinib and venetoclax: practical considerations[11]

- **Can I start ibrutinib on lower dose as I would like to avoid toxicity?**
  The suggested initial dose is 420mg once daily as efficacy has established at this dose and toxicity incidence have not been shown to be dose related.
- **How can I manage grade ≥ grade 3 hematological and non-haematological toxicities?**
  Variable ibrutinib dosing may affect PFS, therefore a recommendation to avoid dose reduction or interruption unless there is a clinical important indication to do so. Dose modification scheme been provided in the ibrutinib SPC which should be followed where possible.
- **My patient is on ibrutinib he will undergo surgery, how I can manage his ibrutinib?**

[14] Goede V et al N Engl J Med 2014;370:1101
[15] Hillmen P et al Lancet 2015;385:1873

For elective surgery: Ibrutinib should be held for 3-7 days pre and post-procedure to allow time to reverse antiplatelets effects (7 days for any procedure that would require sutures or has a high risk of bleeding eg liver biopsy). For emergency surgery, platelet transfusion is recommended.

- **My patient developed atrial fibrillation (AF) after starting ibrutinib, how can I manage it**?

  If a patient develops grade ≥ 3 AF, ibrutinib should be temporarily withheld and AF should be managed by cardiology team by either rate or rhythm control. Drug-drug interaction should be considered if drugs that interact with CYP3A4 been used such as amiodarone. Anticoagulation should be considered based to the European society of cardiology guidelines based on assessment of risk of stroke and bleeding risk (eg CHA_2DS_2-VASc and HAS-BLED scores).[16] Ibrutinib may be restarted after in stable patients together with anticoagulation if required. Warfarin is contraindicated however low molecular weight heparin or direct oral anticoagulants (NOAC/DOAC) may be used.

- **My patient is on aspirin and he need to start ibrutinib, how can I manage it?**

  Aspirin can be continued when treatment is initiated but patient should be closely monitored for any sign of bleeding or easily bruising.

- **My patient had coronary artery stent insertion and is on dual antiplatelet needs to start ibrutinib, how can I manage it?**

  Ibrutinib should not be initiated in patients requiring dual anti-platelet therapy due to the risk of bleeding. Alternative treatment (eg venetoclax) should be considered.

- **My patient is taking ibrutinib and has been started on clarithromycin. What should I do**

  Care should be taken to avoid co-administration of CYP3A4 substrates and prescribers should check for interactions when starting medication for patients treated with ibrutinib. Strong inhibitors should not be used and moderate inhibitors such as clarithromycin should be avoided if possible. If an alternative antibiotic cannot be used then ibrutinib dose should be reduced to 140mg once daily and the patient should be monitored for evidence of toxicity.

- **Concomitant NOACs with ibrutinib, which one I can offer?**

[16] https://www.chadsvasc.org/

Rivaroxaban, apixaban and ibrutinib are all metabolized by CYP3A4 and inhibit p-glycoprotein (P-gp); dabigatran and edoxaban are both inhibit P-gb and are renally metabolized. Concomitant use of these drugs with ibrutinib could lead to increase in ibrutinib plasma concentration although it is unlikely that this is of clinical significance. There are no data to show superiority of one NOAC over another when used with ibrutinib although expert opinion suggests that apixaban or dabigatran may be preferable.[11]

- **My patient is hypertensive and been commenced on ibrutinib which has caused his blood pressure control to deteriorate, how can I manage this?**

  Anti-hypertension medication should be optimised using the joint recommendations outlined by the European Societies of Hypertension/Cardiology.[17] When combining antihypertensive medication, CYP3A4 inhibitors should be avoided.

- **My patient is on ibrutinib and presented with fever, how can I manage my patient?**

  If patient is neutropenic, treat as neutropenic sepsis and consider starting growth factors. Ibrutinib should be paused for patients with grade 4 neutropenia. For non-neutropenic infections, ibrutinib can generally be continued but need to consider pausing for potential drug-drug interaction. For patients with resistant fever consider atypical infections (eg pneumocystis jirovecii or fungus).

- **My patient progress while he is on ibrutinib, what should I do?**

  Patients who progress on ibrutinib especially early in treatment have a greater incidence of Richter transformation; a biopsy and CT-PET scan should be considered if there is clinical evidence to support this. Patients who fail ibrutinib should be considered for eligibility to enter clinical trials and allogeneic transplantation may be considered in younger fit patients. Discussion with a trials/transplant centre is recommended to plan next line therapy.

- **I want to start patient on ventoclax how can assess and manage tumour lysis syndrome (TLS)?**

  TLS is an important identified risk when initiating Ventoclax. This risk was reduced with the recent practiced dosing regimen, prophylaxis usage and

[17] Williams B et al Eur Heart J 2018;39:3021

monitoring measures. Refer to the summary of product characteristics (SPC)[18] for risk assessment and TLS prophylaxis.

- **I am experienced in the management of TLS and my patient has aggressive disease. I would like to start venetoclax at a higher dose level**

  Venetoclax must be initiated according to the SPC in all cases. The onset and kinetic of TLS following venetoclax can be extremely quick and starting at a higher dose can lead to life threatening consequences.

- **My patient on venetoclax has developed neutropenia. Do I need to reduce the dose?**

  Neutropenia is the most frequently occurring adverse reaction following treatment with venetoclax reported in up to two thirds of patients. This normally responds well to GCSF (which may need to be continued usually intermittently eg 3 times per week) and most patients are able to continue treatment without dose modification. Neutropenia associated with venetoclax typically resolves within 6 months of starting treatment.

7.0 Supportive care during CLL treatment

7.1 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 2018 BCSH guidelines for more details[1])

7.2 For patients treated with fludarabine or bendamustine 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

[18] https://www.medicines.org.uk/emc/product/2267

- Aciclovir 400mg bd is recommended, particularly for patients treated with fludarabine containing combination chemotherapy, continued for 6 months following cessation of treatment
- Fluconazole 50mg od or as per local anti-fungal policy
- Hepatitis B/C surveillance using PCR should be performed in patients at risk of viral reactivation. 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.

7.3 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)

7.4 For patients treated with idelalisib

- Aciclovir, GSCF and co-trimoxazole as per section 7.2
- CMV screening prior to treatment is mandatory. All patients at risk of CMV reactivation (CMV IgM positive) must have surveillance (whole blood PCR) during treatment (at each treatment visit) 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 or as per local policy
- Patients developing diarrhoea should have stool cultures to exclude bacterial and viral infections. If negative then the symptoms can often be managed initially with loperamide (2-4 mg qds prn) and/or budesonide (3mg tds). Idelalisib should be discontinued in patients with ongoing diarrhoea ≥ grade 2 (more than 4 stools per day) not responding to treatment

7.5 For patients treated with ibrutinib or venetoclax

- All patients should receive co-trimoxazole as per section 7.2 and acyclovir can be used in accordance with local policy
- G-CSF should be used in patients with treatment related neutropenia to maintain neutrophil count > $1x10^9$/l
- Patients receiving venetoclax should be monitored and treated for tumour lysis syndrome during the first five weeks of therapy as per the guidance in the SPC

8.0 Treatment of relapsed disease

All patients with relapsed disease should be considered for entry into clinical trials. Outside of trials, newer therapies (BCR inhibitors or BCL-2 inhibitors represent the standard of care for all patients). Re-treatment with FCR generally leads to relatively short remission duration (median 2 years)[19] and although this is more effective in patients with a long first remission (eg >5 years),[20] there are concerns about the potential for significant short and long term toxicity. BR is better tolerated than FCR as second line therapy although the efficacy is modest with median PFS of under 24 months.[21,22]

As for primary therapy, treatment is only indicated for patients with progressive or symptomatic disease and choice of therapy should take into account patient age, fitness, co-morbidity and other medication. Optimal sequencing of treatment is uncertain. Published data indicate that venetoclax is an effective treatment option for patients who have failed prior BCRi,.[23,24] although there are fewer data available regarding the efficacy of BCRi in patients who have relapsed after previous venetoclax.[25]

Venetoclax plus rituximab, ibrutinib and idelalisib plus rituximab are all treatment options for patients who have received prior chemo-immunochemotherapy. A number of considerations may be applied to the choice of treatment as in front line therapy (see section 6.3). With regard to the duration of treatment, ibrutinib and idelalisib are both

[19] Awan FT et al Br J Haematol 2014;167:466
[20] Tam CS et al Blood 2014;124:3059
[21] Seymour JS et al N Engl J Med 2018;378:1107
[22] Cuneo A et al Haematologica 2018;103:1209
[23] Mato AR et al Ann Oncol 2017;28:1050
[24] Jones JA et al Lancet Oncol 2018;19:65
[25] Mato AR et al Haematologica 2018;103:1511

recommended for continue until intolerance or disease progression whereas venetoclax plus rituximab is a fixed duration therapy (for 2 years) and results in MRD negative remissions in a proportion of patients. There are however no data currently available directly comparing the outcomes of these regimens to assess any superiority of one regimen over the other.

A suggested treatment algorithm is shown in appendix 2.

9.0 Stem cell transplantation

9.1 Autologous Stem Cell Transplantation (ASCT)

ASCT is not currently recommended for patients with CLL due to a high reported incidence of myelodysplasia / AML and inferior efficacy compared to other treatments.

9.2 Allogeneic Stem Cell Transplantation

The role of allogeneic transplantation (alloSCT) remains unclear in the management of CLL. However, there are emerging data that alloSCT conditioning with reduced intensity conditioning is effective, can overcome adverse risk factors (including 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
- Failed chemo-immunotherapy and BCRi therapy regardless of p53 status
- Refractory or progressed following BCRi therapy with p53 dysregulation.
- PLL (CR1). See section 11.0

  Contact: Dr Adrian Bloor (Christie Hospital)
  Dr Eleni Tholouli (Manchester Royal Infirmary)

10.0 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, venetoclax-R) 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.

10.1 Complete remission

With increasingly effective treatment for patients with newly diagnosed disease, minimal residual disease status is increasingly being used as an endpoint for CLL trials as MRD status has been shown to translate into longer term treatment outcomes.[26]

10.2 MRD monitoring

Several questions remain unanswered:

- Guidelines for MRD monitoring using multi-parameter flow cytometry have been published allowing for standardization of protocols between labs
- Although MRD negativity has been shown to translate into response duration using conventional immune-chemotherapy, this is rarely if ever achieved using newer treatments such as BCR inhibitors. The requirement for MRD negative remissions for long term efficacy with all treatment modalities is uncertain
- Patient selection – potential benefit of achieving MRD –ve remission may be offset by increased toxicity from use of more intensive treatment.
- Routine MRD assessment is currently only recommended in clinical trials.

11.0 Prolymphocytic Leukaemias

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.[27]

[26] Kwok M et al Blood 2016;128:2770
[27] Dearden C Hematology Am Soc Hematol Educ Program. 2015:361

11.1 B-prolymphocytic leukaemia

11.1.1 *Demographics, presentation and immunophenotype*

Typically presents in patients in their 7th decade with a rapidly rising white count, usually >100x10^{9}/l, constitutional symptoms and splenomegaly. 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.

11.1.2 *Prognosis*

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

11.1.3 *Treatment*

There are no ongoing trials for patients with B-PLL and the published literature regarding treatment is small. Most patients require treatment at presentation due to symptomatic disease. 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%.[27] Whether the outcome of treatment can be improved by using combination purine analogue based chemotherapy (eg FC) or using anti-CD20 monoclonal antibodies (Rituximab or Obinutuzumab) is uncertain. Alemtuzumab has some efficacy for treating B-PLL.[28]

There are small series and case reports indicating the BCR inhibitors may be more effective than immunochemotherapy for treating B-PLL although treatment has predominantly been reported for patients with relapsed disease.[29,30]

[28] McCune SL et al Leuk Lymphoma 2002;43:1007
[29] Coelho H et al Case Report Hematol 2017;2017:8563218
[30] Eyre TA et al Br J Haematol 2019;184:667

Younger and fitter patients may be considered for stem cell transplantation in first remission although the efficacy of this approach is uncertain.[31] Splenectomy or splenic irradiation can be considered in patients with massive splenomegaly.

11.1.4 *Conclusions*

Treatment of B-PLL remains suboptimal. Purine analogue based immunochemotherapy is most commonly used treatment as per CLL. BCR inhibitor therapy (eg ibrutinib) should be considered based on the very poor prognosis with standard treatment although this is not routinely funded. Selected younger patients with good performance status may be considered for allogeneic stem cell transplantation.

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

11.2 T-prolymphocytic leukaemia

11.2.1 *Demographics, presentation and immunophenotype*

Patients typically present in their 7th decade with a high circulating white blood count, lymphadenopathy and hepatosplenomegaly. Unlike B-PLL, disease infiltration beyond the blood, bone marrow and spleen is relatively common (eg skin infiltration, conjunctival disease, pleural effusions). 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 the majority of cases; and many cases harbor additional recurrent chromosomal abnormalities (eg chromosome 6, 8, 12p, 17p).[27]

11.2.2 *Prognosis*

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

[31] Kalaycio ME et al Biol Blood Marrow Trans 2010;16:543

11.2.3 *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.[32,33] Responses are however typically short-lived irrespective of the treatment used. Longer term remissions may be achieved using allogeneic stem cell transplantation.[34]

Alemtuzumab is available on a named patient basis. Intravenous treatment (30mg 3x weekly for 12-16 weeks following dose escalation 3mg, 10mg, 30mg in week 1) is recommended as first line treatment for patients with adequate performance status. Subcutaneous administration reduces the treatment related toxicity however is not recommended for this indication due to reduced efficacy.[32] Patients are at risk of opportunistic infections and in addition to the supportive care measures recommended for purine analogue based treatment (see section 7.2) patients require:

- Steroid premedication to reduce the risk of infusional toxicity
- Weekly monitoring for CMV reactivation (if CMV seropositive) for the duration of treatment and for at least 6 weeks following completion of therapy or longer if there is evidence of viral reactivation
- Irradiated blood products

Fludarabine, steroids or supportive care should be considered for patients unfit for Alemtuzumab. Recent reports suggest that venetoclax may be effective for treating T-PLL although confirmatory results of a clinical trial investigating this are awaited.[35]

11.2.4 *Conclusions*

Alemtuzumab is the standard of care for fit patients requiring treatment for T-PLL. 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

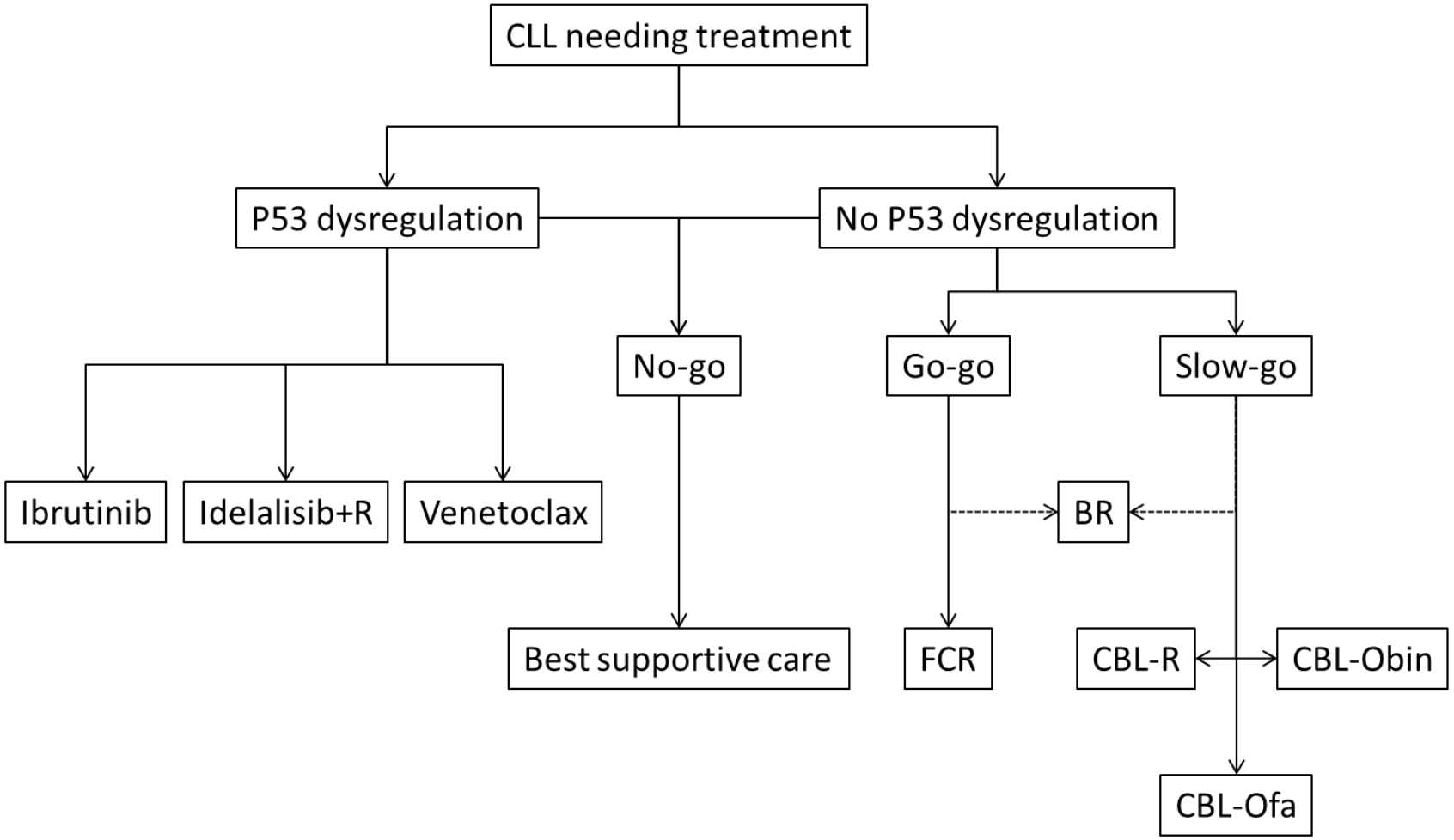
[32] Dearden CE et al Blood 2011;118:5799
[33] Dearden CE et al Blood 2001;98:1721
[34] Wiktor-Jedrzejczak W et al Bone Marrow Transplant 2019;Jan 21:epub
[35] Biodol B et al Blood 2017;130:2499

response was > 12 months. Very preliminary data suggest that venetoclax may be effective for this indication. .

12.0 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 2018 BSCH guidelines contain contact details for many of these.

13.0 Appendix 1 – first line CLL therapy



14.0 Appendix 2 – relapsed CLL therapy