Lymphoma Network of New Zealand

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma Protocol

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

CLL/SLL is a common lymphoproliferative disorder in adults with an incidence of 3-4 per 100,000 per year. It is more prevalent in males and most commonly presents in the 7th decade. There is a familial/genetic predisposition with 10% of patients having a first degree relative with a haematological malignancy.

CLL has not generally been considered curable, although some patients do have prolonged disease free survival with current immunotherapy regimens.

Diagnosis

- In up to 70% of patients the diagnosis of CLL is an incidental finding on a FBC
- The diagnosis of CLL requires ≥ 5 x 10^9 circulating clonal B-cells persisting for 3 months and a characteristic immunophenotype
- CLL cells typically express CD5, CD19, CD23, CD200, weak surface immunoglobulin and weak or absent CD79b, CD22 and FMC7
- Current recommendations suggest that CD19, CD5, CD20, CD23, Kappa and Lambda are mandatory diagnostic markers in CLL, and CD79b and CD200 are recommended markers.
- CD200 is recognized as the best discriminator between CLL and mantle cell lymphoma
- Cases with an atypical immunophenotype should have FISH for t(11:14) undertaken to exclude mantle cell lymphoma
- In cases where CLL has atypical features, LEF1 is a SPECIFIC immunohistochemical marker for CLL, with positivity seen in 100% of cases
- Patients with a clonal lymphocyte count between 3 and 5 x 10^9/L in the absence of lymphadenopathy, splenomegaly or cytopenias are classified as monoclonal B lymphocytosis with a risk of progression to CLL of 1-2% per annum. There is a prevalence of 3.5% in subjects >40 years. The 10 year survival of patients with MBL does not differ from age and sex matched controls
- In SLL excision lymph node biopsy is recommended with adequate immunophenotyping to establish a diagnosis: CD3, CD5, CD20, CD23, CD10, cyclinD1
- There is no current indication to screen family members for the presence of a circulating clonal B cell population or for a genetic susceptibility

Table 2: Distinguishing between CLL, monoclonal B cell lymphocytosis (MBL) and small lymphocytic lymphoma (SLL)

Criteria	CLL	MBL	SLL
Clonal B lymphocytes > 5	Y	N	N
Disease related cytopenias	Y/N	N	N
B symptoms	Y/N	N	Y/N
Lymphadenopathy/splenomegaly	Y/N	N	Y

Monoclonal B cell lymphocytosis (MBL)

- As the diagnosis of MBL has no survival impact, immunophenotyping analysis to establish this diagnosis is not recommended if the ALC (Absolute Lymphocyte Count) is less than 7 provided the peripheral blood morphology is consistent with CLL, there are no unexplained cytopenias and there is no clinical evidence of lymphadenopathy or organomegaly
- Most patients express the same immunophenotype as CLL. Higher CD38 expression could indicate a higher risk or progression

Small Lymphocytic Lymphoma (SLL)

- SLL is a lymphoma where the malignant cells have the immunophenotype and morphology as for CLL

CLL

- The lymphocytes in CLL have a distinct morphology and are small with a high N:C ratio and condensed nuclear chromatin. Prolymphocytes are medium in size with a lower N:C ratio and a prominent nucleolus
- Prolymphocytes, cells with irregular nuclear contours and larger cells with more dispersed nuclear chromatin may be present but account for <15% of the lymphoid cells. Cases with a higher proportion of these atypical cells are often associated with trisomy 12
- >55% prolymphocytes defines B-PLL

Management in Primary care and Indications for Referral

In up to 70% of patients the diagnosis of CLL is an incidental finding on full blood count (FBC). In asymptomatic patients with no anaemia or thrombocytopenia urgent assessment via the 62 day Faster Cancer Treatment (FCT) pathway is usually not necessary. In most centres GPs can be referred to localized CLL pathways that give immediate advice on management of low risk patients who do not need to be seen urgently, as well as criteria for specialist assessment. See http://aucklandregion.healthpathways.org.nz/ for an example of a clinical pathway for lymphocytosis and CLL.

Initial Investigations

EVALUATION AT PRESENTATION

History

- History of infections, B symptoms: weight loss and night sweats
- Family history of lymphoid malignancy
- Performance status
- Detailed history of significant comorbidities

Physical Examination

- Measure and record (preferably diagrammatically) lymphadenopathy/splenomegaly/hepatomegaly
- Details of a full general medical examination

Initial Laboratory Investigations

- Full blood count and peripheral blood film
- Cell markers for diagnostic immunophenotype if not already performed (Peripheral blood EDTA tube)
- FISH studies: These should be performed at the time the patient requires treatment and are not recommended at diagnosis in patients who do not require therapy outside of clinical trials. In SLL patients FISH studies should be performed on the initial biopsy.
- DAT and reticulocyte count +/- haemolysis screen if indicated. A positive DAT is predictive of haemolysis, especially in those who receive fludarabine.
- Routine biochemistry, urate and LDH
- Serum immunoglobulins and protein electrophoresis
- β_2 microglobulin
- Hepatitis serology including HepBcoreAb in all patients receiving anti B cell monoclonal antibody therapy prior to treatment
- Pregnancy testing prior to chemotherapy in women of childbearing age
- Bone marrow aspirate and trephine is not usually necessary at diagnosis but is indicated in cases with atypical features or to rule out other causes of anaemia/thrombocytopenia. It is often performed prior to initiation of treatment, but is not essential

Radiological Investigations

- CT scans are not required for initial investigation outside clinical trials, but should be performed in cases of SLL, and be considered if bulky intra-abdominal lymphadenopathy is suspected clinically

Staging

Staging is based on clinical parameters and not on specialised laboratory investigations.

Two staging systems are widely used: the Binet and the Rai, which has been modified to reduce the number of prognostic groups from 5 to 3.

Stage A patients who have Hb>100g/L, lymphocytes<30 x 10^9/L, minimal or no lymphadenopathy, non-diffuse pattern of BM involvement and a lymphocyte doubling time >12 months have an 80% chance of being alive at 10 years and only 15% are likely to require treatment.

Neither the original Binet or Rai staging systems distinguished between ITP/AIHA or marrow infiltration as a cause for anaemia or thrombocytopenia when classifying a patient as having Stage C or high risk disease. However cytopenias due to autoimmune causes should not be considered when assigning clinical stage to patients and other causes of anaemia should also be excluded.

Table 3: Staging in CLL

Binet Stage	Features	Median survival (months)
A	<3 lymphoid areas	>120
B	>3 lymphoid areas	84
C	Haemoglobin < 110 g/L or platelets <100	24

RAI stage	Risk group	Features	Median survival (months)	Median survival Mayo series (months)
0	Low	Lymphocytosis only	>120	143
I		Lymphadenopathy	95	125
II	Intermediate	Hepatomegaly/splenomegaly	72	100
III/IV	High	Haemoglobin < 110 g/l or platelets < 100 x 10^9/L	30	57/63

In both staging systems the presence of lymphadenopathy and splenomegaly or hepatomegaly is based on clinical exam and not CT scans or ultrasound.

Note that SLL can be staged using the Lugano modification of the Ann Arbour staging system.

Ann Arbour staging system for SLL

I	Involvement of a single lymph node or lymphoid structure (spleen, thymus, Waldeyer's ring)
II	Two or more regions on the same side of the diaphragm
III	Two or more regions on both sides of the diaphragm
IV	Involvement of extranodal sites (such as liver, lung or marrow) not due to direct extension from a nodal site
X	Bulky Disease ▪ 10 cm maximal dimension of a nodal mass, or ▪ Mediastinal mass > 1/3 internal transverse diameter of the thorax measured at the level of T5/6 intercostal space on PA CXR.
E	Involvement of a single extranodal site, adjacent to a known nodal site.
	Tonsils, Waldeyer's ring and spleen are considered nodal tissue

Prognosis in CLL/SLL

Whilst the clinical stage provides some prognostic information, 75% of patients are now diagnosed at Rai 0/Binet Stage A disease so additional prognostic information is needed to assess the risk of progression. Recognised poor prognostic factors include:

- Advanced stage, male gender, peripheral blood Lymphocyte Doubling Time < 12 months
- Raised β2 microglobulin (> 4 mg/L), high LDH
- Cytogenetic abnormalities – 17p abnormalities, loss or mutation of TP53

Cytogenetic Changes	Median Survival (in months)
Normal	111
13qdeletions	133
Trisomy 12	114
11q deletions	79
17p deletions	32

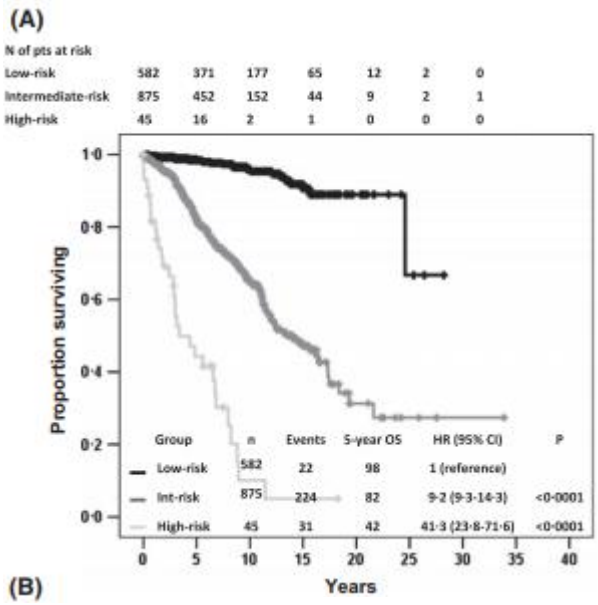
Source: Dohner NEJM 2000

- Unmutated *IGHV* gene status (40% of patients) – Median survival 8 years vs 25 years. Not routinely available in New Zealand. Conversely fit patients with mutated *IGHV* treated with FCR chemotherapy can have long term (>10 year) disease free survival
- CD38 expression >20%
- Cd49d expression>30%
- Lymphocyte doubling time < 12 months
- Diffuse bone marrow infiltration
- A number of molecular markers including mutations of p53, NOTCH1, SF3B1 and BIRC3 have been identified and a molecular 'prognostic index' proposed

MDACC Prognostic Score: Assess score using the patient and laboratory parameters below

Risk Group	Score	Median time to treatment (years)	5 year survival
Low	1-3	11 to NR	97%
Intermediate	4-7	5 to 9.4	80%
High	>7	0.1-0.7	55%

Biomarker	Score
Age	
< 50 years	1
50-65 years	2
>65 years	3
Sex	
Male	0
Female	1
Rai Stage	
0-II	0
III-IV	1
Involved nodal areas	
<3	0
3	1
Lymphocyte count	
< 20 x 10^9/L	0
20-50 x 10^9/L	1
>50 x 10^9/L	2
B2-microglobulin	
< 3.2mg/L	0
3.2 – 6.4 mg/L	1
>6.4 g/L	2

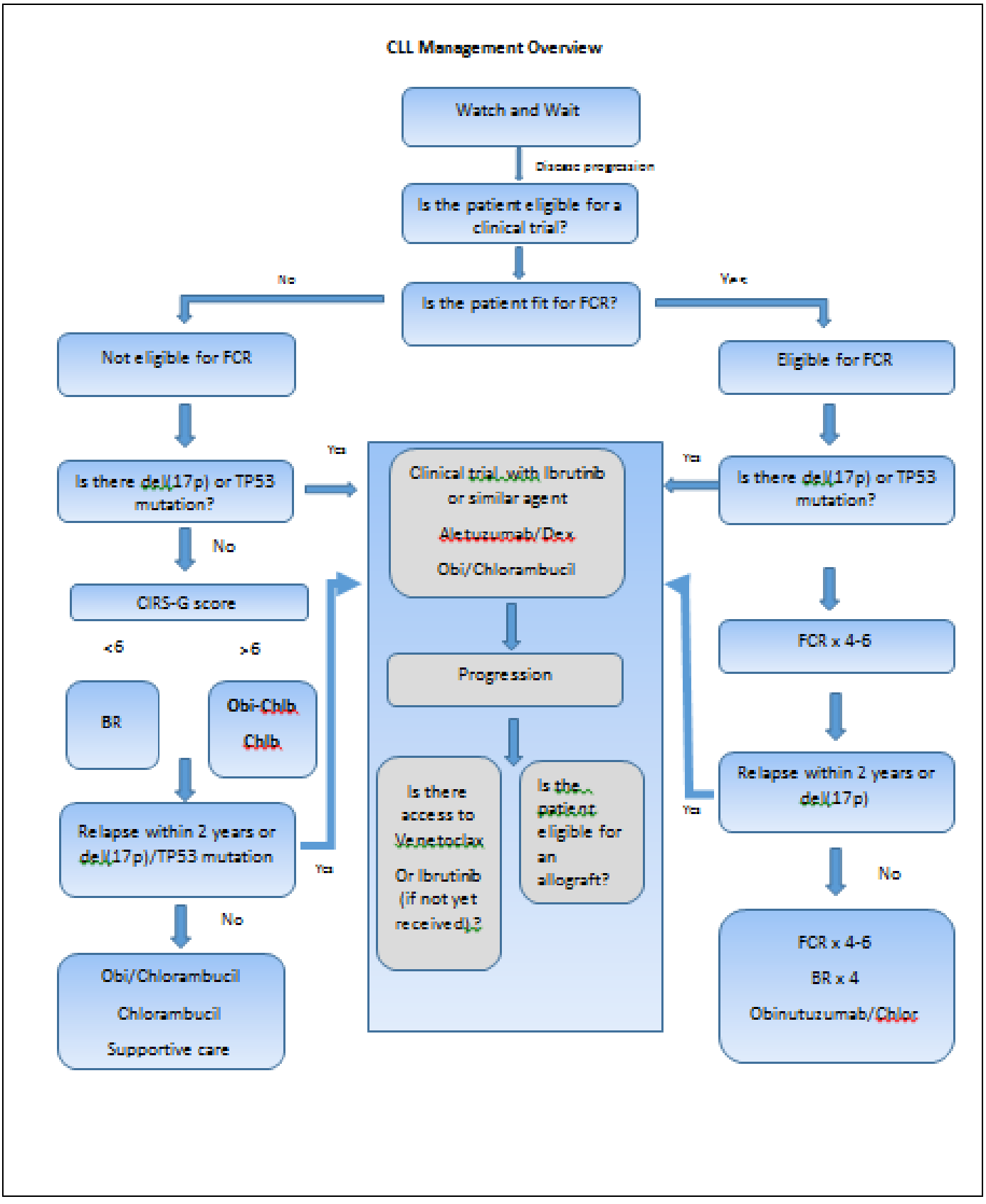


Overall survival in CLL patients

CLL-IPI

The CLL-IPI has recently been published and assigns risk scores to patients on the basis of 5 molecular and clinical parameters, dividing patients into 4 prognostic groups. Its utility in routine practice is limited currently by availability of *IGHV* mutation analysis.

		Hazard ratio	Assigned risk score
TP53 status/17p deletion by FISH	Deleted or mutated/17p deleted	4.2	4
IGHV mutational status	Unmutated	2.6	
B_2 microglobulin	>.5 mg/L	2.0	2
Clinical stage	Rai 1-IV or Binet B-C	1.6	1
Age	>65	1.7	1
CLL IPI risk score	Median overall survival	5 year overall surviva	10-year overall survival
0-1	NR	93.2%	79%
2-3	105 months	79.3%	39.2%
4-6	75 months	63.3%	2.9%
7-10	29 months	23.3%	3.5%


CLL Management Overview
Watch and Wait
Disease progression
Is the patient eligible for a clinical trial?
Is the patient fit for FCR?
No
Yes
Not eligible for FCR
Eligible for FCR
Is there del(17p) or TP53 mutation?
Yes
No
CIRS-G score
<6
>6
BR
Obi-Chlb
Chlb
Relapse within 2 years or del(17p)/TP53 mutation
Yes
No
Obi/Chlorambucil
Chlorambucil
Supportive care
Clinical trial with Ibrutinib or similar agent
Aletuzumab/Dex
Obi/Chlorambucil
Progression
Is there access to Venetoclax
Or Ibrutinib (if not yet received)?
Is the patient eligible for an allograft?
Yes
Is there del(17p) or TP53 mutation?
Yes
FCR x 4-6
Relapse within 2 years or del(17p)
Yes
No
FCR x 4-6
BR x 4
Obinutuzumab/Chlor

Pre-Treatment Evaluation

Decisions around the type of therapy depend on the fitness of the patient, rather than age, but there are no standardized criteria by which to judge fitness in CLL patients. In clinical trials fitness has been assessed using the performance status (ECOG), an assessment of comorbidities (the CIRS scale - http://eforms.moffitt.org/cirsgScore.aspx) and renal function.

Important pre-treatment factors that need to be considered include:

- Patient factors: age, performance status, co-morbidities, renal function
- Disease related factors: Severity of symptoms, speed of progression, prognostic factors, especially TP53 abnormalities
- Treatment related factors: degree and duration of response to prior therapy, any potential contraindications and likelihood of significant side effects

First-Line Treatment Options

All patients should be considered for available front line trials. Treatment is broadly stratified according to patient's fitness for therapy and presence of 17p deletion

a. **Fit patients with normal renal function and no significant comorbidities**

FCR chemotherapy. Some clinical trials have used a CIRS score of <6 to help determine eligibility for FCR

b. Intermediate patients: (>70, renal impairment, CIRS score < 6)

Bendamustine and Rituximab

c. **Older unfit patients:**

The CLL11 trial has demonstrated that Chlorambucil in combination with Obinutuzumab gives the best PFS and OS in this population and should be considered standard first line therapy in elderly patients.

Very co-morbid patients may be best treated with chlorambucil monotherapy or supportive care alone

d. **Patients with 17p deletion or TP53 mutations:**

At the current time a clinical trial is the best option for this group of patients

- Ibrutinib (not currently funded) should be considered standard first line therapy in this

population

- Venetoclax (not funded)
- Alemtuzumab and dexamethasone or methylprednisolone is an option if other drugs are not available and this combination is preferable to chemotherapy. See http://www.bloodjournal.org/content/124/21/1991
- Obinutuzumab and chlorambucil could be considered in patients who fulfil the SA criteria for obinutuzumab
- FC

In transplant eligible patients early referral to the local transplant team is recommended to allow early identification of a possible donor.

Table 4: Response rates and PFS with standard regimens

Regimen	CR (%)	ORR (%)	Median PFS (months)	Median TTNT
FCR	40.7	97	51.8	
BR	31.5	97.8	43.2	
Chlorambucil/Obinutuzumab	22.2	75.5	26.7	42.7 months
Chlorambucil/Rituximab	8.3	65.9	15.7	32.7 months
FC	38.0	94.0	32.8-40.0	
Chlorambucil monotherapy	0	30.2	10.9-20	
Data from CLL4 trial, CLL8 trial, CLL10 trial: Note that these patient groups differ and one cannot directly compare PFS of different regimens across studies.				

SLL with localized Lugano Stage 1 disease: Involved site radiotherapy 24 Gy

BCR Inhibitors and BCL2 Inhibitors

a. IBRUTINIB is an oral inhibitor of Bruton's tyrosine kinase and causes irreversible inhibition of B cell pathways which normally promote cell proliferation and survival. In clinical trials it has been shown to be superior to ofatumumab in relapsed/refractory patients and in de novo patients with 17p deletion. The pivotal trial results can be viewed at http://www.nejm.org/doi/full/10.1056/NEJMoa1400376#t=article and http://www.bloodjournal.org/content/124/21/327.

The FDA granted accelerated approval to Ibrutinib for relapsed/refractory patients in 2014

Ibrutinib is recommended for the following groups of patients:

1. All newly diagnosed patients with 17p deletion or p53 gene mutations
2. Patients who have relapsed within 2 years of FCR therapy
3. Patients who have received 2 prior lines of therapy and are considered inappropriate for retreatment with a fludarabine based regimen

- Recommended dose: 420 mg daily. Treatment is continuous until disease progression or unacceptable toxicity
- Major adverse events include: Diarrhoea (36%), Fatigue (30%), Cough (24%), atrial fibrillation (7.6%), grade 3-4 neutropenia (14%) and major haemorrhage (4.9%)
- An ECG is recommended as baseline prior to initiation of Ibrutinib
- Patients at risk of tumour lysis syndrome should receive prophylaxis with allopurinol/rasburicase and be monitored closely
- Regular monthly monitoring of FBC and LFTs is recommended
- Caution is recommended with the use of anticoagulants and anti-platelet agents. Warfarin use was not permitted in the clinical trials with this agent, and many clinicians recommend therapy with a DOAC instead
- If surgery is required withhold treatment with Ibrutinib for 3 to 7 days pre and post-surgery
- Grapefruit and Seville oranges should not be consumed during Ibrutinib treatment as they contain inhibitors of CYP3A. Dosage adjustment is recommended when using CYP3A inhibitors such as erythromycin, fluconazole, ciprofloxacin etc
- A reversible increase in lymphocyte counts has been observed during the first few weeks of ibrutinib therapy. Lymphocytosis associated with ibrutinib should not be considered progressive disease in the absence of other clinical findings. It is often associated with a reduction in lymphadenopathy
- Antiviral and PJP prophylaxis is recommended

Dose Modifications

Toxicity Occurrence	**CLL dose modification after recovery**

1st	Restart at 420 mg daily
2nd	Restart at 280 mg daily
3rd	Restart at 140 mg daily
4th	Discontinue

Myelosuppression

Toxicity	**Ibrutinib dose**
Grade 4 neutropenia (ANC < 0.5 x 10^9/L or Grade 3 neutropenia (ANC 0.5-1.0) with infection or fever	Hold until ANC greater than 1. Restart at dose indicated above
Grade 4 thrombocytopenia (platelets<25) or Grade 3 (platelets < 50) with bleeding	Hold until platelets greater than or equal to 50 and restart at dose indicated above
Non-haematological toxicity ≥ 3	**Hold util improvement to grade 1 or baseline and restart at dose inicated above**

Hepatic impairment

Heatc impaiment	**Recommended dose**
Mild (Child-Pugh Class A)	140 mg po daily
Moderate (Child-Hugh Class B)	280 mg daily
Severe (Child-Pugh Class)	Not recommended; hepatic impairment is associated with coagulopathy and may increase the risk of bleeding

Renal impairment

No adjustment recommended in mild or moderate renal impairment.

For additional information see:

http://www.medsafe.govt.nz/profs/datasheet/I/Imbruvicacap.pdf

c. VENETOCLAX

This oral bcl-2 inhibitor is highly active in CLL and an effective drug in patients with 17p deletion and relapsed/refractory disease. The overall response rate in this setting is 80% with complete response recorded in 20%. It is currently only available in clinical studies or on a compassionate basis. See “Targeting Bcl2 with

Venetoclax in Relapsed CLL" http://www.nejm.org/doi/full/10.1056/NEJMoa1513257#t=article

Response evaluation after treatment

CT scans are not recommended in routine practice for staging or follow-up evaluations

- A bone marrow to confirm a CR can be performed at the discretion of the treating consultant. It should be performed a minimum of 2 months post treatment
- The measurement of minimal residual disease (MRD) in blood or bone marrow following therapy has become an important prognostic marker for measuring PFS and OS. Recent studies have demonstrated that the long-term outcome of patients is similar after either 4 or 6 cycles of FCR, as long as their marrow shows no MRD
- Minimal Residual Disease (MRD) assessment: Peripheral blood can be used, but needs to be performed at least 2 months post treatment. MRD negativity is associated with longer response duration and survival

Definitions of Response	
Remission	**Features**
Complete Remission (CR)	No symptoms
	No hepatosplenomegaly/lymphadenopathy (by physical exam =/- CT)
	Normal FBC (haemoglobin 110, neutrophils>1.5, platelets >100
	▪ Above should be maintained for 2 months after which a marrow should show < 30% lymphocyte and no lymphoid nodules. If lymphoid nodules then patient has a nodular PR ▪ If patients remains anaemic or thrombocytopenic but is otherwise in CR then classify as PR
Partial Remission (PR)	>50% decrease in peripheral blood lymphoctyes and >50% decrease in lymphadenopathy and/or splenomegaly
	The above should be maintained for 2 months in conjunction with

	one or more of the features below: ▪ Hb>100 or >50% improvement from baseline ▪ Neutrophils>1.5 or >50% improvement from baseline ▪ Platelets > 100 or >50% improvement from baseline ▪ With lymphocytosis: systemic response and improvement in haemoglobin and platelets (Ibrutinib)
Progressive Disease (PD)	>50% increase in the sum of the products of >2 nodes on at least 2 determinations carried out 2 weeks apart and/or ▪ >50% increase in liver and/or spleen size ▪ >50% increase in lymphocyte count to at least 5 x 10^9 ▪ Transformation to a more aggressive histology ▪ Certain therapies (for example those interfering with B cell receptor signalling) may cause blood lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count by itself, does not uniformly indicate an increased tumour burden, but may rather reflect a redistribution of leukemic cells from the lymphoid tissues to the blood. In such cases increased peripheral blood lymphocytosis is not a sign of treatment failure
Stable Disease	Patients who do not fulfil criteria for CR, PR or PD

Relapsed Disease

A watch and wait approach can be adopted again until there is an indication for therapy.

For bulky relapse with systemic symptoms consider biopsy to exclude high grade transformation.

Genetic assessment for acquisition of 17p deletion or TP53 gene mutation should be considered in order to determine most appropriate second line treatment.

Chemotherapy options are the same as those for first line therapy and the choice will depend on patient age and the duration of response to first line therapy

- **All patients should be considered for appropriate relapsed/refractory clinical trials**
- Treatment options following initial treatment depend on response to first line therapy and tolerability. If responses to first-line therapy were good (>3 years for chemo-immunotherapy), then first-line therapy can be repeated. Rituximab is funded in this setting for relapse 36 months post therapy, and Obinutuzumab

can also be utilized

- Those patients with a PFS less than 3 years following chemo-immunotherapy should be considered for treatment with one of the novel agents in a clinical trial - e.g. Ibrutinib or other BCR Inhibitors, or the bcl-2 inhibitor Venetoclax
- Oral chlorambucil is suitable for older unfit patients
- CHOP or CHOP like therapies are less effective than purine analogues in patients previously treated with chlorambucil but do have activity in patients relapsing after purine analogues
- High dose methyl-prednisone, splenectomy, and radiotherapy may all be considered as palliative therapy for late-stage refractory patients

Management of Common Disease Related Complications

. a. **Auto-immune haemolytic anaemia or thrombocytopenia**

- AIHA is reported in 10-20% of CLL patients and ITP in 2-5%. Pure red cell aplasia and autoimmune neutropenia are rarer but probably under recognised. Patients with underlying haemolysis should avoid fludarabine. AIHA or ITP should be treated before deciding whether therapy for CLL is needed
- Patients with AIHA or ITP should be treated according to guidelines for idiopathic AIHA or ITP
    - Folate supplementation
    - Prednisone at 0.5-2mg mg/kg/day body weight per day for 2-4 weeks, tapering off over several weeks
    - Red cell transfusion should be avoided if possible, but may be needed in severe anaemia. Note that cross matched blood may be delayed
    - for ITP IVIg 1 gm/kg as a single infusion or 0.4 mg/kg over 5 days can be used if immediate response is required
    - Cyclosporin may be indicated in resistant cases or to maintain response and allow withdrawal of steroids. Commence 5 mg/kg/day for 6 days then reduce to 3mg/kg/day and maintain serum level 100-150
    - For patients not responding to corticosteroids Rituximab 375 mg/m^2 weekly x 4 is a reasonable option prior to splenectomy
    - Splenectomy
    - A history of AIHI should not be considered a contraindication to FCR as it is associated with a very low rate of haemolysis (<1%)

The Binet or Rai staging systems do not distinguish between ITP/AIHA or marrow infiltration as the cause for

anaemia or thrombocytopenia that results in classifying a patient as having stage C or high-risk disease.

Autoimmune conditions affecting non-haematological tissues are rare, but described and can be precipitated by therapy. These include:

- Bullous pemphigoid/paraneoplastic pemphigoid
- Angioedema
- Churg-Strauss syndrome
- Polyneuropathy
- Ulcerative Colitis
- Vasculitis

b. Infection

- Infective complications are common and account for the majority of CLL deaths
- Susceptibility is multifactorial and due to the disease itself, hypogammaglobulinemia, impaired T and natural killer cell function and defective complement activity
- All patients should receive vaccination against encapsulated bacteria (pneumococcus and HIB) and annual influenza vaccination, but NOT live vaccines (including the current shingles vaccine). Vaccination is recommended 6 months post treatment to allow time for immune reconstitution.
- Patients presenting with infection or unexplained PUO, even in the absence of neutropenia should routinely have a full sepsis screen

Table 5: Antibiotic Prophylaxis and Vaccinations in Patients with CLL

Local supportive care measures should be implemented in patients receiving treatment. The following table is a guide only.

Treatment	Possible Infection	Antibiotic Prophylaxis	Vaccine	Other
All patients			Pneumococcal and Haemophilus influenza vaccines at diagnosis. **Live vaccines including BCG, MMR, zoster and varicella vaccine contraindicated** Annual Flu vaccination	
Fludarabine, bendamustine or B cell monoclonal antibody; Ibrutinib HepBcoreAb Positive	Hepatitis	Lamivudine 100 mg daily for the duration of chemotherapy and 6 months afterwards	n/a	Avoid if possible in patients with known prior hepatitis B infection – consult with hepatology
Fludarabine or bendamustine based treatment Alemtuzumab Ibrutinib	PJP	Cotrimoxazole 960 mg MWF or Cotrimoxazole 480 mg daily If allergic to cotrimoxazole alternatives include nebulised Pentamadine 300 mg 4 weekly Or Dapsone 100 mg twice weekly	n/a	Start at commencement of treatment and continue for minimum 6 months post treatment
Alemtuzumab Fludarabine or Bendamustine based treatment	VZV CMV	Valaciclovir 500 mg od Valganciclovir pre-emptive therapy for increased PCR	n/a	NB: Interaction of bendamustine and acyclovir CMV monitoring by PCR every 1-2 weeks

Splenectomy	Encapsulated bacteria	Penicillin or Amoxicillin	Refer to Splenectomy Guidelines on vaccination; Pneumococcus Haemophilus influenza Meningococcus	

c. Secondary hypogammaglobulinaemia

Up to 70% of patients with CLL have hypogammaglobulinemia and IVIg (0.5 gm/kg every 3 to 4 weeks) is recommended for those with recurrent severe infections despite prophylactic antibiotics. Monitor IgG levels and maintain trough IgG level in the normal range.

Role of Allogeneic Transplant

In the era of B cell receptor therapies the role of allogeneic stem cell transplant is uncertain. It may still be considered for young patients with 17p deletion or patients with high risk features such as relapse within 24 months of purine analogue combination chemo-immunotherapy, who have achieved a remission with Ibrutinib or Venetoclax.

Richter's Transformation

- Richter's transformation occurs when a patient with CLL then develops a lymphoma. Laboratory tests show that in approximately half the cases the lymphoma arises from the CLL clone. In those lymphomas that are clonally unrelated, the outcome is more consistent with that of de novo diffuse large B cell lymphoma
- Occurs in 2-8% of patients with CLL and usually has rapid progression in a single nodal site accompanied by a rise in LDH
- It is very important to consider this possibility and arrange appropriate biopsy to confirm. Use of PET scan in this situation can assist in directing the best site for tissue biopsy
- Rarely transformation to classical Hodgkin's lymphoma can occur
- Refer to the local lymphoma MDM for discussion of treatment options. R-CHOP is considered standard

therapy in most patients with DLBCL transformation, and subsequent ASCT often recommended.

- In clonally unrelated transformation the median survival is 5 years compared to a median survival of 8 to 16 months in clonally related transformation
- In clonally related transformation consider ASCT consolidation or RIC-allo SCT in suitable patients

Follow-Up and Survivorship

- FBC and clinical examination every 3-12 months
- Regular evaluation for secondary malignancies – there is a sevenfold increased risk of both solid cancers and secondary haematological malignancies
- Advice re sun protection

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Changes made to CLL protocol after LNZ meeting:

1. Substitution of "CLL/SLL is a common lymphoproliferative disorder in adults" for most common leukemia in the introduction

2. Insertion of a comment re the mandatory markers needed for a diagnosis of CLL. Current recommendations suggest that CD19, CD5, CD20, CD23, Kappa and Lambda are mandatory diagnostic markers in CLL, and CD79b and CD200 are recommended markers.
   Reference: Reproducible diagnosis of Chronic Lymphocytic Leukemia by flow cytometry: an European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) harmonisation project. Rawstrom A., et al. Cytometry B Clin Cytom 2017

3. In the section on MBL insertion of the following comment: "As the diagnosis of MBL has no survival impact, immunophenotyping analysis to establish this diagnosis is not recommended if the ALC (Absolute Lymphocyte Count) is less than 7 provided the peripheral blood morphology is consistent with CLL, there are no unexplained cytopenias and there is no clinical evidence of lymphadenopathy or organomegaly."

4. Removal of the distinction between CLL and CLL/PL

5. Insertion of a comment that a positive DAT is predictive of haemolysis, especially in those who receive fludarabine

6. Change of SLL is staged using the Lugano modification to SLL can be staged…..the discussion at the meeting indicated that this staging system is infrequently used in NZ for staging SLL, but one or two people were using it

7. Addition of CIRS score and clinical trials into the flow chart for therapy

8. Inclusion of CIRS score < 6 into the Intermediate patient category eligible for Bendamustine – to align with the existing special authority criteria

9. Addition of Venetoclax and FC to possible options for 17 p deleted patients as discussed at the meeting, emphasising that a Clinical Trial is the preferred option for this group of patients

10. Tidied up table of supportive care options and inserted a comment that local guidelines should be followed