# Haematology Cancer Clinical Guidelines

Haematology Expert Advisory Group (EAG)
on behalf of Northern Cancer Alliance

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SECTION 9

# GUIDELINES FOR MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) AND LYMPHOPROLIFERATIVE DISORDERS

Written by Dr Scott Marshall, Haematology Consultant Sunderland, July 2018

## Reliable Sources for Patient information

The national patient support associations are a valuable resource for patients and have internet sites and booklets with reliable information (Bloodwise: https://bloodwise.org.uk/info-support/chronic-lymphocytic-leukaemia/what; CLLSA: https://www.cllsupport.org.uk/; Leukaemia Care: https://www.leukaemiacare.org.uk/; Macmillan: https://www.macmillan.org.uk/information-and-support/leukaemia/chronic-lymphocytic).

## Investigation of asymptomatic lymphocytosis

- Routine requesting of immunophenotyping for the investigation of asymptomatic lymphocytosis should only be requested when the total lymphocyte count is greater than $10x10^9$/L.
- Full blood count monitoring every 3-6 months should be recommended for those who are asymptomatic and have a total lymphocyte count < $10x10^9$/L.
- Symptomatic patients or patients with lymphocytosis and associated cytopenias or patients with lymphadenopathy/hepatosplenomealy should be investigated as clinically indicated following clinical assessment.

## CHRONIC LYMPHOCYTIC LEUKAEMIA

### Diagnostic Criteria

A definitive diagnosis of CLL is based on the combination of a lymphocytosis and characteristic lymphocyte immunophenotype.

Scoring system for the diagnosis of CLL

| marker | score: 1 | score: 0 |
|---|---|---|
| CD5 | positive | negative |
| CD23 | positive | negative |
| FMC7 | negative | positive |
| SmIg | weak | strong |
| membrane CD22/CD79b | weak | strong |

Scores for CLL range from 3 to 5 and non-CLL cases from 0 to 2.

### Prognostic factors

| factor | low risk | high risk |
|---|---|---|
| Cytogenetic abnormalities | ▪ None<br>▪ del 13q (sole) | ▪ loss/ mutation of p53*<br>▪ del 11q23 |
| ZAP-70 | ▪ negative | ▪ positive |
| IgVH gene status | ▪ mutated | ▪ unmutated |
| CD23 | ▪ - | ▪ negative |
| Richter's transformation | ▪ - | ▪ present |

*p53 abnormalities predict a poor response to alkylating agents, purine analogues and rituximab monotherapy but not to high-dose steroids or alemtuzumab.

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| Factor | Frequency (stage A patients) | Median time to treatment (years) | Median survival (years) |
|---|---|---|---|
| None | >50% | >5-10 | >15-20 |
| 17p deletion | 4-7% | <1 | 2-4 |
| 11q deletion | 10-15% | 1-2 | 6-9 |
| Germline $IgV_H$ (>98%) | 25-40% | <4 | 8-9 |
| ZAP-70 expression | 20-50% | 3-4 | 8-10 |
| CD38 expression | 25-40% | <4 | 8-10 |

## Investigations

### Baseline investigations

1. Full blood count
2. Immunophenotyping of peripheral blood lymphocytes
3. Renal and liver biochemistry (including urate level)
4. Calculation of Binet/ Rai stage

### Other recommended investigations

1. Serum Immunoglobulins – consideration of IvIg replacement
2. Pneumococcal and HiB immunity testing with vaccination in those not immune
3. Direct antiglobulin test (DAT) and reticulocyte count are essential in all anaemic patients and before starting treatment.
4. Bone marrow aspirate and trephine biopsy if:
    - phenotypically atypical CLL (atypical morphology and low CLL score)
    - for investigation of cytopenias
5. Lymph node biopsy is indicated if:
    - the diagnosis is uncertain from the peripheral blood and bone marrow examinations.
6. CT-scans/US is indicated:
    - where the finding of intrathoracic or bulky intra-abdominal disease would influence the need for, or choice of, therapy
    - if the presence of splenomegaly is uncertain on physical examination
    - to determine remission status following treatment in patients with bulky nodes prior to therapy
7. FISH cytogenetics on peripheral blood for 17p (p53) loss/mutation, 11q23 abnormality (ATM), chromosome 12/ trisomy 12 and del 13q.
    - at time of requiring treatment as a minimum in patients fit for intensive treatment.
    - Consider performing at diagnosis in young patients to help advise on likely prognosis

## Staging of CLL

Binet stage

A < 3 lymphoid areas*
B > 3 lymphoid areas
C Hb < 10 g/dL or platelet < $100x10^9$/L

*The five lymphoid areas comprise unilateral or bilateral cervical, axillary and inguinal lymphadenopathy, hepatomegaly and splenomegaly.

## Management of CLL

All newly diagnosed patients with CLL should have their management defined by a formal Multi-Disciplinary Team Meeting.

### Monoclonal B-lymphocytosis (CLL phenotype) – MBL-CLL

MBL-CLL is defined as the presence of a CLL immunophenotype with lymphocyte count $<5x10^9$/L and no lymphadenopathy or organomegaly.

These patients should have their blood counts, constitutional symptoms, lymph node enlargement, liver and spleen size monitored every 3 to 6 months in the first year and, if stable, annually thereafter. The regular follow-up can be performed in the local haematology clinic or by the patient's general practitioner

### Early stage (Binet A) CLL

Treatment is not indicated for patients with early stage CLL regardless of the prognostic markers at presentation.

Patients with low risk CLL (see Prognostic factors) are monitored as MBL-CLL.

Patients with high risk CLL should be monitored every 3 months in the haematology clinic. Only after a period of time with stable disease, should the intervals between patient's follow-up visits be extended.

### Advanced stage CLL requiring therapy (Binet B and C)

= WCLL2008 criteria used for trials

- Progressive marrow failure due to bone marrow infiltration by CLL
  - Haemoglobin <10 g/dL
  - Platelets $<100 \times 10^9$/L
- Massive or progressive lymphadenopathy (cluster >10 cm diameter)
- Massive (>6cm below costal margin) or progressive splenomegaly
- Progressive lymphocytosis >50% increase over 2 months or lymphocyte doubling time <6 months
- Systemic symptoms:
  - Weight loss >10% in previous 6 months
  - Fever >38°C for >2 weeks in the absence of infection
  - Extreme fatigue – cannot work or unable to perform usual activity = ECOG 2 or worse
  - Severe night sweats in the absence of infection
- Autoimmune cytopenias which are poorly controlled by corticosteroids

## TREATMENT OF CLL

# ALL PATIENTS SHOULD BE CONSIDERED FOR ELIGIBILITY TO CLINICAL TRIALS – see trials section

### Supportive Management at all stages of disease

- Annual flu vaccine
- Check Immunity to Pneumococcus + HiB & vaccinate if not immune
- Treatment of auto-immune cytopenias as for patients without CLL
- Antimicrobial prophylaxis / immunoglobulins if recurrent infections
- **SHOULD NOT RECEIVE FOSTAVAX (LIVE)SHINGLES VACCINE BECAUSE OF IMMUNOCOMPROMISE**
- New ”dead”vaccine likely to be available in late 2018, FDA approved Oct 2017 = Shingrix
- Shingrix is more than 90% effective at preventing shingles and post herpetic neuralgia in all age groups.
- Zostavax only 51% reduction of shingles and 67% PHN - less effective in people aged 70 and older.

### Recommendations for initial therapy in CLL

The choice of therapy should be judged according to the desires of the patient, performance status, co-morbidities and potential drug side-effects.

- Patients identified to have TP53 disruption are unlikely to respond well to chemoimmunotherapy. Tests for*TP53* disruption should be performed on all patients prior to each line of therapy, should include both mutation and deletion detection (GRADE IB) and ideally should also reveal subclonal*TP53* mutations (GRADE IIA).
    - Currently in the Northeast, TP53 mutation screening is not routinely available (only as a research test), but can be requested from Oxford Haematology lab which is funded by Janssen Pharmaceutical company
- Analysis of the IGHV mutation status should also be considered (GRADE III). - Retrospective studies have suggested that the sub-group of patients with mutated IGHV genes experience prolonged remissions with chemoimmunotherapy.
- All patients should be screened for HIV/ Hep B and Hep C and appropriate supportive therapy initiated if positive prior to commencing therapy. Advice from Infectious disease/ hepatologist as indicated

### Treatment of Fit patients without disruption of TP53

1) FCR is current Gold standard first line therapy for those adequately fit to receive it. German CLL8 trial has demonstrated improved Progression free survival, overall survival and early evidence suggests that some patients with mutated immunoglobulin gene (low risk) CLL may be “cured” of their disease (Fischer et al, Blood, Jan 2016, Thompson et al, Blood, Jan 2016) in retrospective analysis

**F**ludarabine 24 mg/$m^2$ oral for 5 days (breakfast time)
**C**yclophosphamide 150 mg/$m^2$oral for 5 days (lunchtime)
**R**ituximab 500 mg/$m^2$IV infusion (375 mg/m2 for cycle 1)

28 Day cycle, aim to give 6 cycles. Blood products must be irradiated.
If WCC >30, then rituximab dose should be split over 2 days (100mg on day1, the rest on day 2)

2) Bendamustine/ Rituximab is recommended in patients for whom fludarabine combination chemotherapy is not appropriate e.g. renal impairment, more advanced age, concerns with

marrow capacity or patient preference. Outcomes of BR not far behind FCR. May be more beneficial for patients to receive full dose BR which is associated with less toxicity rather than abbreviated/ attenuated FCR although this has not been tested in a direct head to head clinical trial.

Bendamustine/ Rituximab combination
Bendamustine 70-90mg/m2 IV infusion over 30-60 mins on days 1,2
Rituximab 500mg/m2 IV infusion (375mg/m2 for cycle 1)

28 day cycle, aim to give 6 cycles. Blood products must be irradiated

**Treatment of Less fit patients without TP53 disruption**

1) Chlorambucil is indicated for elderly patients and those with significant co-morbid conditions considered inappropriate for fludarabine combination therapy.
    - Chlorambucil 10mg/m2 od orally for 7 days of 28 day cycle, continue up to 12 cycles according to response/ tolerance. Prolonged treatment is associated with longer PFS – median about 12 months.

2) Addition of anti-CD20 immunotherapy to chlorambucil therapy as above improves responses and PFS and should be considered current standard of care

    Options: a) Rituximab is not recommended because of better effect of b and c

    b) add Ofatumumab 300mg IV day 1, 1000mg day 8 of cycle 1, then 1000mg day 1 of each subsequent cycle
        - 6 to 12 cycles as tolerated
        - Median PFS 23 months (Complement 1 trial)
        - Minimal additional toxicity, well tolerated

    c) add Obinutuzumab 1000mg – type 2 anti-CD20 antibody
        - IV cycle 1 days 1/ 2(dose divided), day 8, day 15, then day 1 for subsequent cycles
        - 6 cycles as per German CLL 11 trial
        - Median PFS 31 months (NB lower dose of chlorambucil used)
        - Time to next treatment 51 months– may offer prolonged treatment free interval to frail population
        - Increased infusion reactions seen in CLL 11 trial – can be managed by stopping BP medication and use of Methylpred or dexamethasone because reactions do not respond to hydrocortisone as used for other anti-CD20 agents
        - Well tolerated in the frail elderly trial population
3) Bendamustine/ Rituximab might be considered as an alternative
4) Ibrutinib is an appropriate treatment option but is not currently funded for this indication

**Treatment of Extremely Frail patients**

1) Single agent chlorambucil may be used in patients who are intolerant of anti-CD20 antibodies or when intravenous therapy is considered unsuitable (GRADE IV).
2) Corticosteroid monotherapy can be considered (GRADE IV).
3) Rituximab monotherapy is not recommended (GRADE IV).
4) Utility and side-effect profiles of B-cell receptor signalling pathway inhibitors in extremely frail patients have not been evaluated in clinical trials and they are not NICE-approved in front-line therapy of standard risk CLL (GRADE IV).

**Treatment of TP53 deleted or mutated CLL**

1. B cell Receptor Signalling Pathway Inhibitors (BCRi)
    - Ibrutinib is the treatment of choice in front-line therapy for patients withTP53 disruption and is now NICE approved (GRADE IB).
        - 420mg once daily

    - Not recommended if on warfarin (caution with other anticoagulants) because ibrutinib associated with impaired platelet function
    - Not recommended if significant heart disease – significant risk of hypertension and arrhythmias
    - Care needed if concomitant CYP3A4/5 inhibitors (eg antifungals, antivirals, clarithromycin, erythromycin, anti-arrythmics – see SPC
    - Treatment should be continued
- Idelalisib and rituximab combination therapy is a suitable alternative for patients for whom ibrutinib is deemed inappropriate, such as patients with significant cardiac disease or patients receiving vitamin K antagonists, and is also NICE approved (GRADE IB).
    - Idelalisib is continued longterm until disease progression – standard dose 150mg bd
    - Rituximab IV 375mg/m2 week1, 500mg/m2 weeks 3, 5, 7, 9, 11, 15, 19
    - Risk of autoimmune side-effects in addition to increased infections– rashes, colitis, pneumonitis which tend to occur in the first 6-12 months. Early diarrhoea common and may settle through dose interruption and reintroduction
- In patients who are otherwise gaining apparent clinical benefit, clinicians should avoid early withdrawal of BCRi (Grade IB).

2. Venetoclax (bcl-2 inhibitor) is a treatment option in patients unsuitable for BCRi

**Relapsed but not refractory CLL (fludarabine-sensitive relapse) – patients fit for further chemoimmunotherapy**

all patients at relapse should have TP53 mutation/ deletion testing and considered for appropriate therapy if positive

- Patients who have a progression free interval of more than 3 years after fludarabine combination or Bendamustine therapy can be considered for FCR if they are fit for further chemoimmunotherapy
- Bendamustine is not funded as a second or subsequent line therapy
- Currently Obinutuzumab and Ofatumumab are only funded as first line therapy. Therefore rituximab is the only anti-CD20 antibody treatment which can be considered for second line and subsequent therapies in combination with chlorambucil but BCRi therapy should be considered in such patients.

**Treatment of Relapsed/ Refractory CLL**

- Idelalisib with rituximab or ibrutinib monotherapy are the treatments of choice for patients with CLL who are refractory to chemo-immunotherapy, have relapsed after chemoimmunotherapy, or for whom re-treatment with chemoimmunotherapy is inappropriate as defined above. In England, for both ibrutinib monotherapy and idelalisib with rituximab, patients need to meet specific NHS England criteria, based on the respective clinical trial inclusion criteria – see relevant guidance (GRADE IB).
- The addition of bendamustine to these BCRis is not recommended (GRADE IV).
- Venetoclax in combination with rituximab might also become an option for BCRi naïve patients (Grade IB).
- Re-treatment with chemoimmunotherapy may be considered as an option for fit patients with CLL who relapse after a prolonged remission (GRADE III).
- Venetoclax is the treatment of choice for patients who fail BCRi therapy and is currently funded through the NHS England Cancer Drugs Fund (GRADE III).

**Allogeneic haemopoietic stem cell transplantation (allo-HSCT)**

- Allogeneic stem cell transplantation (alloSCT) is a treatment option for patients with CLL who have either.
    - failed chemoimmunotherapy and BCRi therapy irrespective of TP53 status.
    - harbour a TP53 disruption and have not responded or lost response to BCRi therapy (GRADE III).
- AlloSCT should be considered for all eligible patients with Richter transformation (GRADE III).

| Factors favouring allogeneic transplant | Factors favouring Novel agents against CLL |
|---|---|
| Higher disease risk | Lower disease risk |
| Complex karyotype<br>High risk Cytogenetics (17p-, TP53 mut)<br>MRD positive<br>Short duration of response<br>Richter's transformation | No high risk cytogenetics<br>Longer duration of prior response<br>MRD negative |
| Lower transplant risk | Higher transplant risk |
| Younger age<br>No comorbidities<br>Well-matched donor | Older age<br>Significant comorbidity<br>Mismatched donor |

**Clinical Trials**

The UK has an excellent reputation for the delivery of high quality clinical trials overseen by the UK CLRN CLL Clinical trials committee. The trial portfolio is constantly evolving.

Please contact Dr Scott Marshall to discuss current availability of trials in the Northeast scott.marshall3@nhs.net

There are multiple new therapies with potent action coming available in CLL that we hope to bring to the Northeast in clinical trials eg Ibrutinib, GS1101 (CAL-101). For any trials not available locally, many more are available in Leeds and can be accessed via Prof Peter Hillmen. peter.hillmen@nhs.net

**Current trials open in the Northeast**

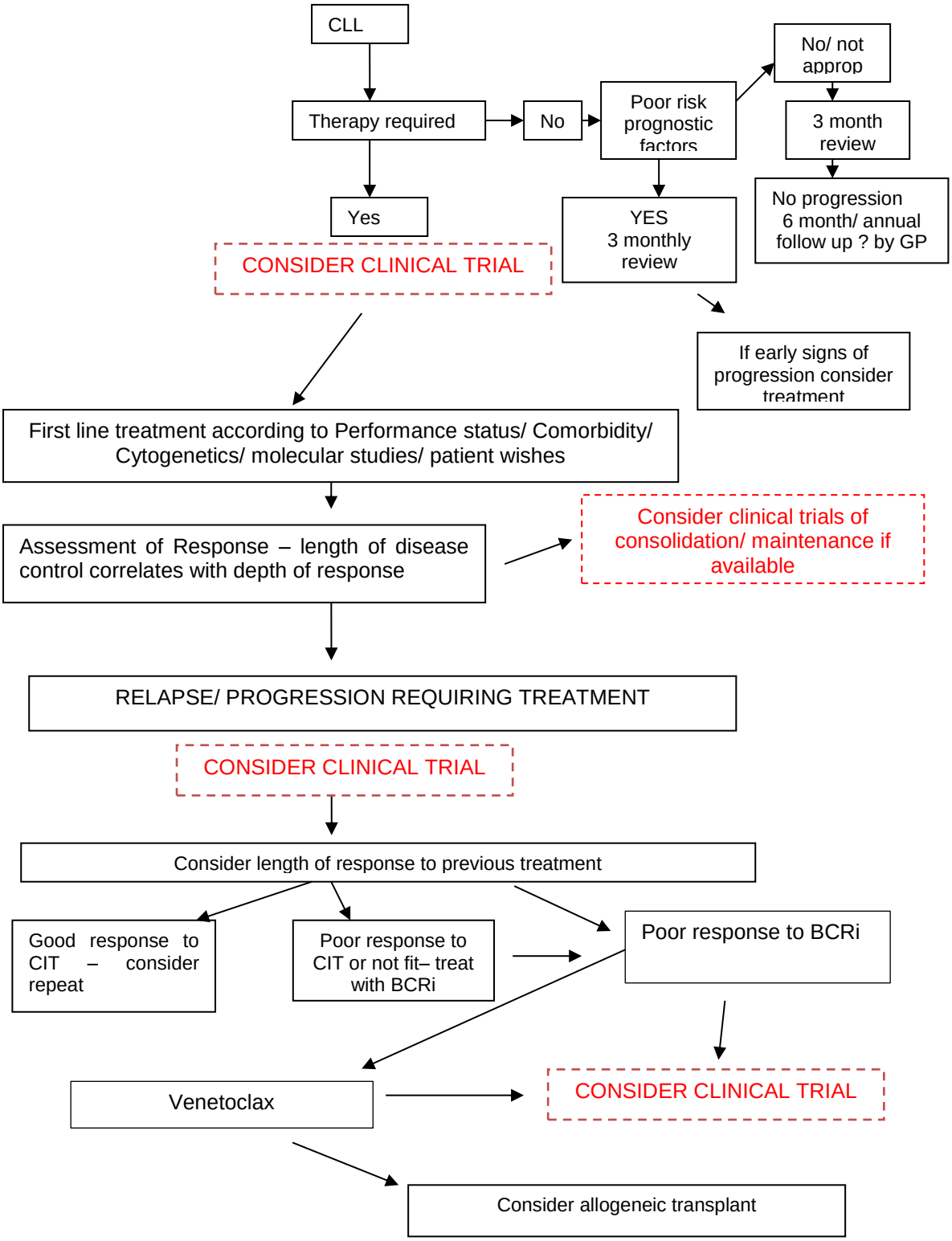
1) FLAIR trial – front line treatment of CLL in patients fit for Fludarabine therapy
    - Open at Gateshead – only centre in Northeast
    - New treatment arms have been opened and others closed to keep contemporary
    - FCR vs ibrutinib vs Venetoclax/ ibrutinib– uses MRD to assess disease response
2) BGB 3111 – front line in elderly (>65yrs) or unfit for FCR
    - Open at Sunderland
    - BGB 3111 vs Bendamustine/ Rituximab. Patients in BR arm can cross-over to new drug at disease progression
    - BGB 3111 is a BTK inhibitor more potent than ibrutinib). Dose = 80mg 2x daily. Low rates of side-effects seen with ibrutinib and well tolerated
    - TP53 mutation/ deleted CLL accepted and will receive BGB 3111

**Summary of CLL Trials Portfolio (July 2018):**

| | Recently Closed Trials in follow-up | Currently Open or soon to OpenTrials | Future Planned Trials |
|---|---|---|---|
| Patients considered fit for FCR (previously untreated) | Bloodwise IcICLLe (Ibrutinib)<br><br>Bloodwise TAP (CALiBRe [Idelalisib monotherapy]) | CLL10 (FLAIR amendment) – Phase III FCR vs Ibrutinib monotherapy vs Ibrutinib+venetoclax | - |
| Patients considered unfit for FCR (previously untreated) | Acerta ACE-007 (Chl+obinutuzumab vs ACP-196+obinutuzumab vs ACP-196)<br><br>RiAltO (Chl-Of vs Benda-Of) | BGB-3111-304_CLL_Phase_3 (BGB-3111 vs chl+obinutuzumab) | Ibrutinib+venetoclax vs Chl+obinutuzumab JNJ-54179060 (GLOW) |
| 17p deleted CLL (previously untreated) | Gilead CLL 312-0133 Study – idelalisib + rituximab in 17p del front-line<br><br>Acerta ACE-007 (Chl+obinutuzumab vs ACP-196+obinutuzumab vs ACP-196) | BGB-3111-304_CLL_Phase_3 (BGB-3111) | FLAIR amendment |
| Consolidation/Maintenance | GALACTIC (CLL8; Obinutuzumab consolidation) | - | INTERRUPT Trial |
| Stage A CLL | CLEAR<br><br>Bloodwise TAP CyCLLe | - | - |
| Richter's Transformation | CHOP-OR (CLL211)<br><br>NCRN 3130: Acerta | - | STELLAR: ACP-196 Bloodwise TAP Trial |

| | | | |
|---|---|---|---|
| | ACE-CL-001: Phase 1, of ACP-196 in CLL | | |
| Relapsed/ Refractory CLL | Bloodwise IcICLLe amendment (Ibrutinib + obinutuzumab)<br><br>Bloodwise CLARITY (Ibrutinib + venetoclax)<br><br>Bloodwise TAP (CALiBRe [Idelalisib])<br><br>Acerta ACE-006 (ACP-196 vs ibrutinib) | ATRi + acalabrutinib study (ACE-CL-110 | ?Bloodwise ACALA_CLLTrial |
| Relapsed 17p del CLL | Bloodwise IcICLLe amendment (Ibrutinib + obinutuzumab)<br><br>Bloodwise CLARITY (Ibrutinib + venetoclax)<br><br>ACERTA ACE-006 (ACP-196 vs ibrutinib)<br><br>Bloodwise TAP (CALiBRe [Idelalisib]) | ATRi + acalabrutinib study (ACE-CL-110) | - |
| Relapsed11 q del CLL (T-PLL) | PiCLLe (PARP inhibitor) | - | ?HOVON T-PLL study |

## CLL TREATMENT ALGORITHM

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# HAIRY CELL LEUKAEMIA

**Diagnosis**

1. Cytopenias
2. Splenomegaly
    - Hairy cells in blood or bone marrow. Peripheral blood to be assessed for diagnostic morphology + monocytopenia
    - Bone marrow biopsy with special stains on sections: CD20, DBA44, TRAP

- Flow cytometry on PB or BM cell suspensions with a panel of McAbs:

    - B-cell panel: CD19, CD20, CD22, Smlg
    - HCL panel: CD11c, CD25, CD103, HC2

    - Molecular Studies: assess for presence of BRAF mutation

**Indications for treatment**

1. Systemic symptoms
2. Significant cytopenias (Hb <12 g/dL, Neutrophils <1.5x109/L, Platelets <100x109/L)

**Treatment**

At presentation:

- Cladribine (Litak®) 0.14mg/kg SC daily for 5 days.
- Pentostatin 4 mg/m2 IV every 2 weeks until maximum response plus 1 or 2 extra injections may be used as an alternative.
- If pancytopenic, consider treatment with interferon alfa to improve blood counts before purine analogues, but this is usually not necessary.

All blood products administered are to be irradiated, and *Peumocystis jiroveci* prophylaxis is indicated for at least 6 months after therapy completed or until CD4 count exceeds 200/mm3.

At relapse:

- Repeat administration of initial therapy.
- If resistance develops, the alternative therapy can be used eg Pentostatin if cladribine used previously.

Rituximab 375mg/m2 weekly for 8 weeks is recommended in the current BCSH guidelines (2012), funding for this has been confirmed by NHS-England..

Other treatment options:

- Splenectomy may be considered for
- symptomatic splenomegaly (massive enlargement, pain, infarction, rupture)
- pancytopenia which is still present after other treatments.
- as a temporising measure in symptomatic pregnant women.

The response to splenectomy is maintained for a median of 20 months, approximately one-half have disease progression within five years, and the overall survival at five years is 60 to 70 percent.

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**Clinical trials**

- Vemurafnib is a BRAF inhibitor and has shown to be effective with ORR >90% in relapsed/refractory patients to purine analogue therapy. This treatment is not currently funded
- Moxetumomab pasudotox is a non-chemotherapeutic agent administered IV on days 1,3 and 5 of a 28 day cycle for up to 6 cycles. It is an anti-CD22 recombinant immunotoxin. In a phase III trial in patients with relapsed/ refractory hairy cell leukaemia who were heavily pre-treated ORR rates were 75% with 41% achieving CR. This was reported at EHA and ASCO in 2018 and promises to be a potential therapy of the future. It is currently not funded but marked by FDA for rapid development/ assessment

# T-PROLYMPHOCYTIC LEUKAEMIA

**Diagnostic Criteria**

- Immunophenotype: CD2+, CD3+, CD4+, CD5+, CD7+, TCRαβ+, HLA-DR-.
- Expression of CD52 antigen should be demonstrated in all cases for therapeutic purposes.
- All cases must have TCR gene rearrangement studies.
- High proportion of cases show inv(14) by cytogenetics.

**Primary Treatment**

- Outcomes in T-PLL are poor and patients should be considered for clinical trials if the patient is willing to travel. No current trials open in the Northeast
- Intravenous alemtuzumab should be used as first line therapy for T-PLL – 30mg IV 3 x per week after dose escalation in the first week to complete up to 12 weeks. CMV PCR monitoring and treatment is required as per standard supportive care protocols (LEVEL IIa and GRADE B).
- All eligible patients should proceed to either autologous or allogeneic stem cell transplant in first remission (LEVEL IV GRADE C).
- Drainage of pleural effusion and/or ascites due to T-PLL is recommended at the beginning of treatment to reduce tumour mass.

**Refractory Disease**

- Patients failing to respond should receive the combination of alemtuzumab plus pentostatin 4mg/ m2 IV weekly for 4 weeks then 2 weekly to maximum response or another purine analogue (LEVEL IV GRADE C).

**Relapse Treatment**

- Repeat treatment with alemtuzumab may be appropriate (confirm that leukaemia cells express CD52)
- Low response rates to purine analogues reported but may be considered in refractory patients.

**Clinical Trials**

- Contact Dr Claire Dearden at The Marsden Hospital, London for advice about trials and their availability
- There are plans for a venetoclax + ibrutinib trial in T-PLL in the UK opening in the Autumn of 2018. This follows demonstration that Venetoclax is a potent agent for T-PLL in laboratory studies (Blood July 2018), as well as report of 2 patients with relapsed/ refractory T-PLL who responded to venetoclax (Blood Dec 2017)

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# WALDENSTRÖM MACROGLOBULINAEMIA

Waldenström macroglobulinaemia is a low grade lymphoplasmacytic non-Hodgkin lymphoma seen in association with an IgM monoclonal protein of any concentration. The $MYD88^{L265P}$ mutation is seen in approximately 90% of patients with Waldenstroms or non-IgM-secreting lymphoplasmacytic lymphoma, however this mutation is also found in smaller numbers (~5-10%) of splenic marginal zone lymphoma and IgM MGUS.

**Diagnostic criteria for Waldenström macroglobulinaemia (WM)**

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes showing plasmacytoid / plasma cell differentiation. Intertrabecular pattern of bone marrow infiltration
- Surface $IgM^{+}$, $CD5^{-}$, $CD10^{-}$, $CD19^{+}$, $CD20^{+}$, $CD22^{weak}$, $CD23^{-}$, $CD25^{+}$, $CD27^{+}$, $FMC7^{+}$ , $CD103^{-}$, $CD138^{-}$ immunophenotype

If end-organ damage is present then patients are classified as having Waldenström macroglobulinaemia. Otherwise smouldering WM (IgM >30g/dl and / or marrow infiltration >10%) or IgM MGUS (IgM <30g/dl and <10% marrow infiltration).

Patients are said to have an IgM-related disorder if IgM MGUS and symptoms due to the paraprotein. Such symptoms can include hyperviscosity, cold agglutinins, cryoglobulinaemia, autoimmune disease, neuropathy or amyloidosis.

**Prognosis** is by the ISSWM. Risk factors (1 point for each) are: age >65yr; β2 microglobulin >3mg/L; paraprotein >70g/L; Hb <115g/L and platelets <100 $x10^{9}$/L. Risk is low 0-1 (unless age), intermediate (2) or high (3-5). Five year survival is 87% if low-risk, 68% intermediate or 36% high-risk.

**Treatment**

- BCSH guidance recommends baseline haemophilus influenza type B and pneumococcus vaccination, as well as annual influenza vaccination. Vaccination should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy.
- Therapy should currently be reserved for patients who are symptomatic or in whom there is haematological suppression or clear evidence of disease progression.
- The aim of treatment should be to improve the quality and duration of life with minimal side-effects in the most cost-effective manner. It is not yet clear that achievement of a complete remission confers clinical benefit, and it is possible

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that prolonging therapy to maximal response may increase toxicity without extra benefit.

The BCSH (2014) and IWWM-7 (2014) guidelines both suggest that:

- Rituximab combinations (e.g. DRC, R-bendamustine) are recommended first therapies in patients who can tolerate this treatment. BCSH guidance also suggests fludarabine combinations as possible first-line therapy, although there is concern about toxicity.
- At relapse can treat with similar agents or fludarabine combinations (e.g. R-fludarabine, R-FC, R-cladribine). Consider R-CHOP if evidence of high grade transformation (younger patients should be discussed with a transplant centre).
- Chlorambucil, with or without prednisolone, is often used as the initial therapy for frail or elderly patients. Responses are usually slow but toxicity is minimal providing that the dose is adjusted if cytopenias ensue.
- Rituximab is active in the treatment of WM but associated with the risk of transient IgM flare so should be used with caution in patients with symptoms of hyperviscosity and / or IgM levels >40 g/L.
- Bendamustine is available via the Cancer Drug Fund as first line therapy, or for relapsed / refractory patients who are unable to receive R-CHOP, R-FC or high dose therapy. Since the previous guideline update, bortezomib is no longer available via the CDF.
- Plasma exchange (1-2 treatments of 1.5-2.0 plasma volumes) is indicated for the acute management of patients with symptomatic hyperviscosity symptoms.