Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

Acalabrutinib

Regimen

- CLL – Acalabrutinib

Indication

- First-line treatment of chronic lymphocytic leukaemia (CLL) prior to EU licence and NICE reimbursement through the Early Access Programme (EAP) provided by AstraZeneca. Patient should meet ALL the inclusion criteria and NONE of the exclusion criteria in order to be eligible for this programme.

- Inclusion criteria:

  - Patients has untreated CLL and is either:
    a. 65 years of age or greater, OR
    b. greater than 18 and less than 65 years of age provided that at least one of the following criteria is met:
    i. Creatinine clearance more than or equal to 30 mL/min using the Cockcroft-Gault equation
    ii. A score higher than 6 on the Cumulative Illness Rating Scale-Geriatric (CIRS-G)
  - WHO performance status 0, 1, 2
  - diagnosis of CD20+ CLL that meets published diagnostic criteria (Hallek, et al. CLL 2008) as listed below:
    a. monoclonal B cells (either kappa or lambda light chain restricted) that are clonally co-expressing 1 or more B-cell marker (CD19, CD20, or CD23) and CD5
    b. prolymphocytes may comprise 55% or less of blood lymphocytes
    c. presence of greater than or equal to $5x10^9$B lymphocytes/L (5000/µL) in the peripheral blood (at any point since diagnosis)
  - active disease meeting 1 or greater of the following IWCLL 2008 criteria for requiring treatment

- Exclusion criteria:

  - any previous systemic treatment for CLL (note: prior localized radiotherapy is allowed)
  - known central nervous system (CNS) lymphoma or leukaemia
  - known prolymphocytic leukaemia or history of, or suspected, Richter's syndrome
  - confirmed 17p del and/or TP53 mutations, with eligibility for currently reimbursed novel inhibitor treatment ibrutinib, idelalisib + rituximab or venetoclax in the NHS. Please note: If ibrutinib was received by a patient but discontinued due to intolerance and not due to disease progression, the patient may be eligible to receive acalabrutinib
  - uncontrolled autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), defined as declining haemoglobin or platelet count secondary to autoimmune destruction currently or requirement for high doses of steroids (of more than 20mg daily of prednisone daily or equivalent)
  - corticosteroid use of more than 20mg within 1 week before first dose of acalabrutinib, except as indicated for other medical conditions such as inhaled

steroid for asthma, topical steroid use, or as premedication for administration of acalabrutinib or contrast.

- major surgery within 4 weeks before first dose of acalabrutinib
- history of prior malignancy except for the following:
  a. malignancy treated with curative intent and with no evidence of active disease present for more than 3-years before the Early Access Programme application date and felt to be at low risk for recurrence by treating physician.
  b. adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
  c. adequately treated cervical carcinoma in situ without current evidence of disease.
- significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of this application, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480msec
- unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
- uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment
- known history of infection with human immunodeficiency virus (HIV)
- planned vaccination with live, attenuated vaccines within 4 weeks of first dose of acalabrutinib
- serologic status reflecting active hepatitis B or C infection. Patients with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before access is provided. Patients who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive cannot be provided access.
- history of stroke or intracranial haemorrhage within 6-months of this early access programme application
- history of a bleeding diathesis (e.g., haemophilia, von Willebrand disease)
- requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of acalabrutinib
- requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)
- breast feeding or pregnant
- current life-threatening illness, medical conditions, or organ system dysfunction which, in your opinion, could compromise the patient's safety
- concurrent participation in another therapeutic clinical trial
- requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer
- presence of a gastrointestinal ulcer diagnosed by endoscopy within 3-months of the Early Access Programme application date

Toxicity

Drug	Adverse Effect
Acalabrutinib	Diarrhoea, headache, bruising, fatigue, upper respiratory tract infection, nausea, cough, musculoskeletal pain, pyrexia, neutropenia, anaemia, thrombocytopenia, hypertension, rash and atrial fibrillation.

The adverse effects listed are not exhaustive. Please refer to the relevant investigator brochure for full details.

Monitoring

- FBC, U&Es and LFTs prior to starting treatment and then every twenty-eight days for the first twelve weeks of treatment. Thereafter if counts are stable monitoring may take place every twelve weeks.
- Hepatitis B and C status prior to starting treatment as re-activation is a known adverse effect of treatment
- Ensure adequate cardiac function before and at regular intervals during treatment. Consider a baseline ECG for all patients and an echocardiogram should be conducted in patients with a history of cardiac problems or in the elderly prior to starting treatment.
- Pregnancy testing in women of childbearing potential. A negative pregnancy test must be obtained before starting the treatment.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well. Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if the patient is symptomatic of anaemia or where the haemoglobin is less than 8g/dL.

Prior to prescribing cycle 1 the following criteria must be met:

Criteria	Eligible Level
Neutrophils	Greater than or equal to $0.75x10^9$/L or greater than or equal to $0.5x10^9$/L in patients with bone marrow involvement
Platelets	Greater than or equal to $50x10^9$/L or greater than or equal to $30x10^9$/L in patients with bone marrow involvement
Non-haematological toxicity	NCI-CTC grade 1 or below

For subsequent cycles, dose delay if neutrophils are less than $0.5x10^9$/L or the platelets are less than $50x10^9$/L with bleeding or platelets are less than $25x10^9$/L. Restart treatment once the toxicity has resolved to grade 1 using the dosing table below.

Toxicity Occurrence	Dose modification after recovery
First and Second	Hold acalabrutinib until recovery to Grade 1 or below or baseline; may restart at original dose level
Third	Hold acalabrutinib until recovery to Grade 1 or below or baseline; restart at one dose level reduction (100mg OD)
Fourth	Discontinue

Hepatic Impairment

Liver Function	Ibrutinib Dose Modifications
Child Pugh A (mild hepatic impairment)	No dose adjustment required
Child Pugh B (moderate hepatic impairment)	No dose adjustment required
Child Pugh C (severe hepatic impairment)	Not recommended

Renal Impairment

No dose adjustments are required for patients with mild or moderate renal impairment (eGFR ≥ 30ml/min/1.73m^2, as estimated by the MDRD equation). There are no data in patients with severe renal impairment (eGFR less than 29ml/min/1.73m^2, MDRD) or patients on dialysis. In this latter instance prescribed only if the benefit outweighs the risk, monitor patients carefully for signs of toxicity.

Other

In general for all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. Acalabrutinib may be resumed using the dosing table shown above.

Dose modification for Use with CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended acalabrutinib use
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as antibiotics for up to seven days), interrupt acalabrutinib.
	Moderate CYP3A inhibitor	100mg once daily
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase acalabrutinib dose to 200mg twice daily.

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in Aria)

Drug	Dose	Days	Administration
Acalabrutinib	100mg twice a day	1- 28 (inclusive)	Oral

Dose Information

- Acalabrutinib is available as 100mg capsules.

Administration Information

- Acalabrutinib capsules should be swallowed whole with water at approximately 12 hours apart.
- Acalabrutinib may be taken with or without food.
- If a dose of acalabrutinib is missed by more than 3 hours, it should be skipped, and the next dose should be taken at its regularly scheduled time. Extra capsules of acalabrutinib should not be taken to make up for a missed dose.

Additional Therapy

- Allopurinol 300mg once a day oral for 7 days for the first cycle only.
- Anti-infective prophylaxis with;
  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to acalabrutinib.
- It must be made clear to all staff, including those in the community, that acalabrutinib is should only be prescribed under the supervision of a consultant haematologist or oncologist.
- There are many drug interactions associated with acalabrutinib. Caution is advised when concurrently prescribing agents that affect coagulation or platelet function or that influence the hepatic enzyme system CYP3A.
- Co-administration of acalabrutinib with a proton pump inhibitor, H_2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations. If treatment with a gastric acid reducing agent is required, consider using a H_2-receptor antagonist or an antacid with a two hour gap between doses of acalabrutinib and the gastric protection. Avoid co-administration with proton pump inhibitors.
- Acalabrutinib should be withheld for at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding.
- Grapefruit and grapefruit juice, and Seville oranges, should be avoided while on acalabrutinib.
- Acalbrutinib may increase sensitivity to the sun, wear sun protection.

References

1. Jeff P. Sharman, Versha Banerji, Laura Maria Fogliatto et al. ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naïve Chronic Lymphocytic Leukemia (CLL). *Blood 2019*; 134 (Supplement_1):31. https://doi.org/10.1182/blood-2019-128404.
2. Michael Hallek, Bruce D. Cheson, Daniel Catovsky, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukaemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood 2008*; 111(12):5446-5456. https://doi.org/10.1182/blood-2007-06-093906).

REGIMEN SUMMARY

Acalabrutinib

Cycle 1

Day 1-28 inclusive

1. Acalabrutinib 100mg twice a day oral
   Administration Information
   Oral Chemotherapy
   Acalabrutinib should be swallowed whole with water at approximately 12 hours apart.

   Avoid grapefruit and grapefruit juice, and Seville oranges while on acalabrutinib. Always check for drug interactions.

2. Aciclovir 400mg twice a day oral

3. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
   Administration Instructions
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.

   This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice

4. Allopurinol 300mg once a day oral for 7 days

Cycle 2 onwards

Day 1-28 inclusive

5. Acalabrutinib 100mg twice a day oral
   Administration Information
   Oral Chemotherapy
   Acalabrutinib should be swallowed whole with water at approximately 12 hours apart.

   Avoid grapefruit and grapefruit juice, and Seville oranges while on acalabrutinib. Always check for drug interactions.

6. Aciclovir 400mg twice a day oral

7. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
   Administration Instructions
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
   This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Aug 2020	None	Siow Chin Phua Pharmacist	Dr Andrew Duncombe Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.