SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

IBRUTINIB
CHRONIC LYMPHOCYTIC LEUKAEMIA AND LYMPHOMA

PROTOCOL REF: MPHAICLLHA
(Version No. 2.0)

Approved for use in:

1. First line treatment of chronic lymphocytic leukaemia (CLL) or small lymphocytic leukaemia (SLL) in adults who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy would be unsuitable **(TA429)**
2. Relapsed or refractory CLL or SLL in adults **(TA429)** who have had a least one prior line of therapy.
3. Relapsed or refractory mantle cell lymphoma in adults who:
    a. Have only had 1 previous line of therapy **(TA502)**
    b. Have had ≥2 previous lines of therapy and the 2nd line treatment was initiated before NICE's recommendation in January 2018 and all the current CDF criteria are met (Blueteq request form IBR5)
4. Prior to June 2022 ibrutinib was available for relapsed/refractory Waldenstroms macroglobulinaemia, however approval has subsequently been withdrawn. Patients already established on treatment prior to June 2022, can continue ibrutinib for this indication.

Note that Blueteq registration <u>is required</u> for <u>all</u> indications

Dosage:

CLL / SLL (and existing Waldenstroms macroglobulinaemia patients)

Drug	Dose	Route	Frequency
Ibrutinib	420mg	PO	Daily continuous.

Mantle Cell Lymphoma

Drug	Dose	Route	Frequency
Ibrutinib	560mg	PO	Daily continuous

Continuous therapy until disease progression or unacceptable toxicity.

Administration:

- Take at approximately the same time each day
- Swallow whole with water, tablets should not be crushed, cut or chewed
- Avoid Seville oranges and grapefruit juice.

Emetogenic risk:

Low risk

Supportive treatments:

Allopurinol 300mg daily for first month of treatment

Co-trimoxazole 480mg daily

Dosing in renal and hepatic impairment:

Renal	Hepatic
Dose as in normal renal function Use with caution in patients with a creatinine clearance <30ml/min	Child-Pugh Class A: 280mg daily Child-Pugh Class B: 140mg daily Child-Pugh Class C: Not recommended

Interactions:

- Concomitant use with warfarin is contra-indicated due to bleeding risk. Other antithrombotic agents may be used with caution, but should only be started under specialist supervision
- Concomitant use of strong CYP3A4 inducers including St John's Wort, phenytoin, carbamazepine, rifampicin, and phenobarbital should be avoided as this significantly reduces plasma concentration of ibrutinib. If the benefit outweighs the risk and a strong or moderate inducer must be used, monitor closely for lack of efficacy.
- Avoid concomitant use of moderate (fluconazole, erythromycin, aprepitant, ciprofloxacin, diltiazem, verapamil, amiodarone) or strong (ketoconazole, ritonavir, clarithromycin, itraconzole, voriconazole, posaconazole) CYP3A4 inhibitors where possible
- Where treatment with moderate or strong CYP3A4 inhibitors cannot be avoided they should be used for the shortest time possible and the following dose reductions should be observed;
    - For **strong** inhibitors used short term e.g. ketoconazole, itraconazole, voriconazole, posaconazole and clarithromycin, consider interrupting ibrutinib therapy during duration of inhibitor use (7 days or less) or reducing dose to 140mg daily and monitoring closely for toxicity
    - For **moderate** inhibitors reduce ibrutinib to 280mg daily. Monitor closely for toxicity
    - No dose reductions are necessary for mild inhibitors but patients should be monitored for toxicity
- Grapefruit and Seville oranges may increase ibrutinib levels and should be avoided
- P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP in the liver and increase the exposure of medicinal products that undergo BCRP-mediated hepatic efflux, such as rosuvastatin

Main toxicities:

Common: thrombocytopenia, diarrhoea, neutropenia, anaemia, fatigue, musculoskeletal pain, peripheral oedema, upper respiratory tract infection, nausea, bruising, dyspnoea, constipation, rash, abdominal pain, vomiting, decreased appetite, Grade 3 or 4 non-haematological adverse reactions

Rare: pneumonia, abdominal pain, atrial fibrillation, diarrhoea, fatigue, skin infections.

Unknown: stomatitis, dyspepsia, urinary tract infection, sinusitis, peripheral oedema, pyrexia, asthenia, petechiae, muscle spasms, arthralgia, cough, epistaxis, dehydration, dizziness, headache.

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Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2 onwards	Ongoing
Informed Consent	X			
Clinical Assessment	X	X	X	Prior to every cycle. Can be 3 monthly if stable on treatment
SACT Assessment (including toxicity assessment and PS)		X	X	Prior to every cycle. Can be 3 monthly if stable on treatment
ECG	X			For patients with cardiac history or at risk of cardiac complications
ECHO	X			If clinically indicated
FBC	X	X	X	Can reduce to 3 monthly with stable treatment
U&E & LFTs and calcium profile	X	X	X	Can reduce to 3 monthly with stable treatment
Urate	X			
Bone marrow biopsy	X			If clinically indicated
CT scan	X			If clinically indicated
Height	X			
Weight	X	X	X	
Pregnancy test	X			If clinically indicated
Blood pressure	X	X	X	
Hepatitis B (including surface antigen and HB core antibody) and Hepatitis C testing	X			

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if:-

ANC ≥ 0.5 x 10^9/L without infection / fever	Platelets ≥ 25 x 10^9/L

Follow the steps below if any of the following parameters are met:

ANC < 0.5 x 10^9/L or <1.0 with infection / fever	Platelets < 25 x 10^9/L	Grade 3 non-haematological toxicity

1. Stop treatment until ANC ≥ 1.5 x10^9/L or platelets ≥ 75 x10^9/L or baseline for patient if lower than this

2. On first occurrence restart same dose

3. On reoccurrence, reduce dose as per table below:

Toxicity Reoccurrence	CLL / SLL / WM	Mantle Cell Lymphoma
First	420mg daily	560mg daily
Second	280mg daily	420mg daily
Third	140mg daily	280mg daily
Fourth	Discontinue	Discontinue

GCSF support can be considered, titrate to maintain neutrophils >1.0 x10^9/L.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Haemorrhage: Consider benefit-risk with concurrent antiplatelet or anticoagulant therapies, and of withholding Ibrutinib for at least 3 to 7 days pre and post-surgery depending on type of surgery and risk of bleeding.

Cardiac complications: Ventricular tachyarrhythmia and sudden cardiac death.
Periodically monitor all patients for cardiac manifestations, including cardiac arrhythmia and cardiac failure. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.

- In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered. In patients who develop atrial fibrillation on therapy with ibrutinib a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to ibrutinib are non-suitable, tightly controlled treatment with anticoagulants should be considered.
- Hypertension can occur with treatment – monitor blood pressure prior to each cycle and if blood pressure becomes raised above 140/90 refer to GP for blood pressure management and discuss with consultants as may also need ECHO. Patients with pre-existing hypertension should be referred to their GP prior to commencing therapy to ensure control is optimised. Patients with pre-existing hypertension should have an ECHO prior to starting treatment and if a reduced ejection fraction identified ibrutinib should be used with caution.

Hepatitis B reactivation: establish hepatitis B virus status before initiating ibrutinib and consult a liver disease expert for monitor and management in patients with positive hepatitis B serology.

References:

1. NICE (2017) TA429. https://www.nice.org.uk/guidance/ta426 Accessed 28/04/2020.
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3. NICE (2022) TA795. Ibrutinib for treating waldenstroms macroglobulinaemia. https://www.nice.org.uk/guidance/ta795 Accessed 17/6/22.
4. Janssen-Cilag. Imbruvica 140mg film-coated tablets (Ibrutinib). Summary of Product Characteristics. Updated 14/02/2022. Accessed on 27/07/2022
5. MHRA (2017) Ibrutinib (Imbruvica): reports of ventricular tachyarrhytmia; risk of hepatitis B reactivation and of opportunistic infections. Accessed 28/04/2020
6. Lancet Oncology (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Accessed on 28/04/2020
7. The New England Journal of Medicine (2014). Ibrutinib versus Ofatumumab in previously treated Chronic Lymphoid Leukemia (RESONATE Trial). Accessed 28/4/2020

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
			To be completed by author
	1.1	**Mark Nelson**	**Original document**
	2.0	**Jennifer Gibson**	**Transferred to new template.** **Removed Waldenstroms macroglobulinaemia as commissioned indication (NICE FAD SS2371)** **Updated indications and interactions in line with NICE criteria and SPC**