Ibrutinib [+/- R]

INDICATIONS

1. **CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) / SMALL LYMPHOCYTIC LYMPHOMA (SLL) [ICD-10 code: C91]**
   - First line monotherapy for CLL/SLL with 17p deletion or TP53 mutation [Licensed / NICE approved [TA429] / **BLUETEQ** required]
   - Monotherapy for relapsed / refractory CLL/SLL with 17p deletion or TP53 mutation [Licensed / NICE approved [TA429] / **BLUETEQ** required]
2. **MANTLE CELL LYMPHOMA (MCL) [ICD-10 code: C83]**
   - First line treatment for MCL (with or without rituximab), instead of intravenous chemotherapy [Unlicensed / Previously available via NHSE interim funding during the COVID-19 pandemic / From 1st October 2022 not commissioned for new patients and only funded for patients who started treatment and had BLUETEQ approved for this indication before 1st October 2022 to continue therapy until the patient and their NHS clinician consider it appropriate to stop]
   - Monotherapy for relapsed/refractory MCL in patients who have either received 1 prior line of systemic therapy or been treated with >=2 prior lines if 2nd line therapy was initiated before NICE's recommendation in January 2018 [Licensed / NICE approved [TA502] / **BLUETEQ** required]
3. **WALDENSTRÖM MACROGLOBULINEMIA (WM) [ICD-10 code: C88]**
   - Monotherapy for relapsed / refractory WM [Licensed/ Previously funded via CDF for patients who have received at least 1 prior line of treatment / From 8th June 2022 not commissioned and only funded by the company for patients who started treatment and had BLUETEQ approved for this indication before 8th June 2022 to continue therapy until the patient and their NHS clinician consider it appropriate to stop]

TREATMENT INTENT

Induction and maintenance of remission

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests - FBC, ESR, DAT, U&Es, LDH, urate, calcium, magnesium, creatinine, phosphate, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, HIV 1+2 after consent.
4. Urine pregnancy test – required before first cycle of chemotherapy in women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy. Ensure the pregnancy declaration is signed to confirm that patient must use effective protection against pregnancy from cycle 1 onwards until 6 months following the completion of chemotherapy treatment.

5. ECG +/- Echo and baseline BP in all patients with a cardiac history or at risk of cardiac complications (hypertension, smokers, diabetes)
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
9. Ensure pre-chemotherapy counselling in line with local trust guidelines.
10. Assess and document tumour lysis risk as part of pre-assessment. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8).
11. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

1. IBRUTINIB MONOTHERAPY

Day	Drug	Dose / Indication	Route	Administration details
1	**IBRUTINIB**	420mg OD (**CLL/SLL, WM**)	PO	Take at approximately the same time each day. Swallow tablets whole with water. Tablets available as 560mg, 420mg, 280mg, 140mg (28 pack sizes). See INTERACTIONS section below.
		560mg OD (**R/R MCL**)	PO	
CYCLE FREQUENCY: every 28 days				
DURATION: until disease progression or unacceptable toxicity				

2. IBRUTINIB MONOTHERAPY OR in combination WITH RITUXIMAB [First line treatment for MCL patients who started treatment before 1st October 2022 – see INDICATIONS section above]:

Day	Drug	Dose	Route	Administration details
1	**IBRUTINIB**	560mg OD	PO	Take at approximately the same time each day. Swallow tablets whole with water. Tablets available as 560mg, 420mg, 280mg, 140mg strengths (28 pack sizes). See INTERACTIONS section below.
1	**RITUXIMAB**[a,b]	375mg/m2*	IV	In 500mL sodium chloride 0.9% *[Refer to Protocol Care Plans - Rituximab infusion rates, max 400mg/hour]* [*Cycle 1 IV, then can be switched to SC, see below]
		1400mg**	SC	[**Cycle 2 onwards SC if IV route tolerated at Cycle 1]
CYCLE FREQUENCY: Cycles 1-6: every 28 days; Cycle 7 onwards: every 56 days				
DURATION: Ibrutinib in combination with rituximab for 2 years, followed by ibrutinib monotherapy until disease progression or unacceptable toxicity				

[a] **Pre-medications (30 minutes before rituximab): IV rituximab:** Hydrocortisone succinate 100mg IV, Paracetamol 1g PO, Loratadine 10mg PO [hydrocortisone can be omitted from cycle 2 onwards if no infusion related reactions (IRRs) at cycle 1], **SC rituximab**: Prednisolone 25mg PO, Paracetamol 1g PO, Loratadine 10mg PO [prednisolone can be omitted if no IRRs at cycle 1]

RESTAGING

Clinical response should be assessed monthly for the first 3 months. NB. Patients on ibrutinib will develop worsening of lymphocytosis for the first 8-12 weeks, sometimes considerably longer, and response cannot be assessed by a drop in lymphocytes. Formal re-staging should be performed by CT at 3-6 months. Subsequent CT scans should be considered every 3-6 months.

DOSE MODIFICATIONS

Interrupt ibrutinib for any grade 3 or greater non-haematological, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities. Once symptoms of toxicity have resolved to grade 1 or baseline (recovery), reinitiate ibrutinib at the starting dose. If the toxicity reoccurs, reduce dose by 140 mg. A second reduction of dose by 140 mg may be considered as needed. If toxicities persist or recur following two dose reductions, discontinue ibrutinib.

Toxicity Occurrence	Mantle Cell Lymphoma	CLL/SLL and WM
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

Renal impairment	Recommendation
CrCl ≤ 30 mL/min or on dialysis	No data. Use only if benefit outweighs risks. Monitor closely.

Hepatic impairment	Recommendation
Child-Pugh Class A	280mg daily
Child-Pugh Class B	140mg daily
Child-Pugh Class C	No data

CONTRA-INDICATIONS

Hypersensitivity to ibrutinib, rituximab, or any of the excipients listed in the Summary of Product Characteristics (SmPc).
Use of preparations containing St. John's Wort.
Caution initiating with severe thrombocytopenia and consider platelet support if needed.

INVESTIGATIONS

- FBC, creatinine monthly initially, extending to 3 monthly for stable patients.

Patients who are stable and without any side-effects could be monitored in a nurse-led or pharmacist-led clinic with blood pressure and pulse readings.

CONCURRENT MEDICATIONS

- **Consider for patients at higher risk for TLS and/or opportunistic infections.**

Allopurinol	300mg daily for 7 days [Cycle 1 only] unless otherwise indicated in TLS risk assessment. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8)
Aciclovir (non mandated for ibrutinib monotherapy)	200mg three times daily for duration of treatment and 3 months afterwards
PCP prophylaxis (non mandated in first-line setting)	Co-trimoxazole 480 mg three times a week on Mon/ Wed/ Fri for duration of treatment and for 3 months afterwards (Consider reducing the dose to 480 mg twice weekly during neutropenic periods). PCP prophylaxis should be considered for all relapsed patients with a history of recurrent infections, or on immunoglobulin replacement. **The clinician reviewing the requirement for PCP prophylaxis should document their decision on ARIA.**

EMETIC RISK

Low

DRUG INTERACTIONS

(Note this list is not conclusive. Always refer to the product SmPC and consult with a pharmacist)
Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4 (CYP3A4).

CYP3A4 inhibitors

Avoid concomitant administration of ibrutinib with strong or moderate inhibitors of CYP3A4. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored closely for signs of ibrutinib toxicity.

- **Strong** CYP3A4 inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin), consider interrupting ibrutinib during duration of CYP3A4 inhibitor use or reduce ibrutinib dose to 140mg daily.
- **Moderate** If CYP3A4 inhibitor must be used, reduce the Ibrutinib dose to 280mg daily. Avoid Seville oranges and grapefruit, as these contain moderate CYP3A4 inhibitors.

CYP3A4 inducers

Administration of ibrutinib with inducers of CYP3A4 can decrease ibrutinib plasma concentrations. Avoid concomitant use of strong or moderate CYP3A4 inducers (e.g., carbamazepine, rifampicin, phenytoin). Consider alternative agents with less CYP3A4 induction. Preparations containing St. John's Wort are contraindicated during treatment with ibrutinib.

Anticoagulants

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Use of either anticoagulants or medicinal products that inhibit platelet function (antiplatelet agents) concomitantly with ibrutinib increases the risk of major bleeding. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib and monitor for signs and symptoms of bleeding.

WARNINGS AND SPECIAL PRECAUTIONS

IBRUTINIB – MHRA advice for healthcare professionals:

- cases of ventricular tachyarrhythmia have been reported
- temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular arrhythmia, including palpitations, chest pain, dyspnoea, dizziness, or fainting, and assess benefit-risk before restarting therapy
- be aware of the risk of hepatitis B virus reactivation and establish hepatitis B virus status before initiating therapy
- for patients with positive hepatitis B serology, consultation with a liver disease expert is recommended before the start of treatment; monitor and manage patients according to local medical standards of care to minimise the risk of hepatitis B virus reactivation
- consider prophylaxis according to standard of care for patients who are at an increased risk of opportunistic infections

RITUXIMAB

- Infusion-related reactions, predominantly seen during the first infusion, usually in the first one to two hours. Main symptoms comprise fever, chills and rigors. Other symptoms may include flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome.
- Patients with high tumour burden or with a high number of circulating malignant cells are at risk of cytokine release syndrome. This may manifest as severe dyspnoea, bronchospasm and hypoxia in addition to fever, chills, rigors, urticaria and angio-oedema (usually presents after 1 - 2 hours of infusion).
- Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patient treated with rituximab. Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.
- Consideration should be given to withholding anti-hypertensive medications 12 hours prior to the rituximab infusion due to risk of hypotension with the first dose of rituximab.

ADVERSE REACTIONS

(Consult with pharmacist and refer to SmPC for full details)

IBRUTINIB

- Most common adverse reactions (≥ 20%): thrombocytopenia, diarrhoea, neutropenia, musculoskeletal pain, upper respiratory tract infection, nausea, haemorrhage (e.g., bruising), rash, pyrexia, arthralgia
- Most common grade 3 or 4 adverse reactions (≥ 5%): pneumonia, hypertension, neutropenia, lymphocytosis, thrombocytopenia.
- Cases of atrial fibrillation and atrial flutter have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically 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.

- Hypertension is commonly associated with ibrutinib, and regular monitoring is indicated, ideally using ambulatory monitors. Co-existing hypertension needs proactive management.
- Other adverse reactions: stomatitis, constipation, dyspepsia, urinary tract infection, sinusitis, peripheral oedema, asthenia, petechiae, muscle spasms, epistaxis, dizziness, headache.

RITUXIMAB

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. Hepatitis B reactivation – see pathway for treatment and management of HBV positive patient. [Link]

EXTRAVASATION RISK

Ibrutinib (oral): not applicable
Rituximab: neutral

TREATMENT RELATED MORTALITY

Less than 5 %

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Cheung (Pharmacist)	Updated NHSE commissioning for CLL, PCP prophylaxis review and general formatting	Sep 2018	2.1	May 2020
Faouzi Djebbari (Haematology Pharmacist)	Update with the new indication during COVID-19 pandemic	June 2020	2.2	May 2021
Graham Collins, Haematology Consultant	Addition of information re ibrutinib + rituximab front line	November 2020	2.4	May 2022
Natalia Czub, Haematology Pharmacist, Dr Toby Eyre, Haematology Consultant, NSSG Lymphoma Group	Indications, supportive medications and references updated. Annual protocol review.	July 2022	3.0	July 2024
Natalia Czub, Haematology Pharmacist	Indications updated (MCL 1st line, COVID-19 Interim NHSE funding ceased for new patients)	September 2022	3.1	September 2024