Ibrutinib

Indication

Treatment of relapsed or refractory Mantle Cell Lymphoma in patients who have had only 1 previous line of therapy.
(NICE TA 502)

Treatment of Chronic Lymphocytic Leukaemia after at least one course of chemotherapy, or as first line treatment in patients with TP53 deletion not suitable for chemo-immunotherapy.
(NICE TA429))

Treatment of Waldenstrom's macroglobulinaemia in patients who have had at least 1 prior therapy.
(NICE TA491)

ICD-10 codes

Codes with a prefix C83 and 91

Regimen details

Mantle Cell Lymphoma

Day	Drug	Dose	Route
1 – 30	Ibrutinib	560mg	PO

Chronic Lymphocytic Leukaemia and Waldenstroms Macroglobulinaemia

Day	Drug	Dose	Route
1 – 30	Ibrutinib	420mg	PO

Cycle frequency

Every 30 days, continuously.

Number of cycles

Continued until disease progression or unacceptable toxicity

Administration

Ibrutinib is available as 140mg, 280mg, 420mg and 560mg tablets. .

Tablets should be taken once a day, at approximately the same time each day. They should be swallowed whole with water. If a patient forgets to take a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra tablets to make up the missed dose.

Seville oranges and grapefruit and grapefruit juice should be avoided whilst taking ibrutinib.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential.

Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance <20ml/min) OD for the first cycle
Loperamide if required
Pneumocystis jiroveci prophylaxis as per local policy

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
Clotting studies	14 days
U + E (including creatinine)	14 days
LFTs	14 days
Blood pressure	14 days
Hepatitis core antibody and surface antigen	14 days
Hepatitis C antibody	14 days
HIV 1 and 2 status	1 month
CT staging of disease	2 months

Bone marrow biopsy (at consultant discretion)

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	48 hours (monitor 4 weekly)
U + E (including creatinine)	48 hours (monitor 4 weekly)
LFTs	48 hours (monitor 4 weekly)
Blood pressure	Monthly or as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	> 35 x 10^9/L
Creatinine clearance	> 30mL/min
Bilirubin	< 1.5 x ULN

It is important to note that patients on ibrutinib will experience a worsening of lymphocytosis for the first 8-12 weeks and response cannot be assessed by drop in lymphocyte count.

Dose modifications

Toxicity occurrence	Ibrutinib dose (MCL)	Ibrutinib dose (CLL or WM)
First	560mg OD	420mg OD
Second	420mg OD	280mg OD
Third	280mg OD	140mg OD
Fourth	Discontinue	Discontinue

- **Haematological toxicity**

Withhold ibrutinib for any grade ≥ 3 neutropenia with infection or fever, or grade 4 haematological toxicity. Once toxicity resolved to grade 1 or baseline, re-start ibrutinib at the original dose. For further occurrences the dose should be reduced as per the dosing table above.

- **Renal impairment**

No dose modifications required for patients with mild-moderate renal impairment (CrCl> 30mLmin). There is no information on ibrutinib in patients with severe renal impairment or on dialysis; use with caution.

- **Hepatic impairment**

Ibrutinib is metabolised by the liver. In hepatic impairment the dose should be modified as below:

Degree of hepatic impairment	Ibrutinib dose
Mild (Child-Pugh A)	280mg OD
Moderate (Child-Pugh B)	140mg OD
Severe (Child-Pugh C)	Not recommended

Child Pugh Classification:

Score	1	2	3
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
PT (s prolonged)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

The individual scores are summed and then grouped as:

- <7 = A
- 7-9 = B
- >9 = C

- **Other toxicities**

If any grade ≥ 3 toxicity, withhold ibrutinib until resolved to grade 1 or baseline. Restart as per the dosing table above.

Toxicity	Definition	Dose adjustment
Haemorrhage	Unexpected bleeding	Discontinue
Bleeding risk pre and post-surgery	3 days prior to until 7 days post-op	Withhold Ibrutinib
Infection	Fever and constitutional upset	Withhold Ibrutinib

Hypertension

The prevalence of hypertension is reported to increase with longer duration treatment (≥ Grade 3 4% year 0-1, 9% year 4-5). Regularly monitor blood pressure and initiate or adjust antihypertensive medication as appropriate.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Haemorrhage (subdural haematoma, GI bleeding, and haematuria)
Renal toxicity
Secondary primary malignancies
Cardiac arrhythmias
Cerebrovascular events
Interstitial lung disease
Viral reactivation

- **Frequently occurring side effects**

Myelosuppression
Atrial fibrillation
Epistaxis
Abdominal pain
Pneumonia, upper respiratory tract infection
Diarrhoea
Nausea, vomiting
Rash
Hypertension

- **Other side effects**

Fatigue
Musculoskeletal pain
Peripheral oedema
Cough
Dizziness
Headache

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin and other vitamin K antagonists are contra-indicated during ibrutinib treatment.

Strong or moderate CYP3A inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) - avoid concomitant use, and consider alternative agents. If strong CYP3A inhibitors cannot be avoided consider interrupting ibrutinib therapy for duration of inhibitor use (up to 7 days).

Avoid concomitant use of strong CYP3A inhibitors which need to be taken chronically (e.g. ritonavir, indinavir, nelfinavir, saquinavir).

If a moderate CYP3A inhibitor is used (e.g. fluconazole, erythromycin, diltiazem, atazanavir, imatinib, verapamil, ciprofloxacin), reduce the ibrutinib dose to 140mg for the duration of inhibitor use.

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

Seville oranges, grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of ibrutinib.

Strong CYP3A inducers (e.g. carbamazepine, rifampin, phenytoin and St. John's Wort) **–** avoid concomitant use, may decrease ibrutinib plasma concentration.

Additional comments

Ibrutinib can cause foetal harm in pregnant women. Advise women to avoid becoming pregnant. Not known whether Ibrutinib is excreted in human milk.

Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding.

References

- Summary of Product Characteristics Ibrutinib (Janssen-Cilag), accessed 24 January 2020 via http://www.medicines.org.uk
- National Institute for Clinical Excellence (NICE) TA429. Accessed 24 January 2020 via www.nice.org.uk
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- Byrd JC, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukaemia. *N Engl J Med* 2014; 371: 213-223.
- Wang M, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med 2013*; 369: 507-516.
- Treon, S et al ; Ibrutinib in previously treated Waldenstroms Macroglobulinemia. NEJM 2015 ; 372 : 1430 – 1440

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Date: March 2020