NHS
North West Coast
Strategic Clinical Networks

IBRUTINIB

INDICATION:
Relapsed Chronic Lymphocytic Leukaemia (CLL) or CLL with a 17p deletion or TP53 mutation
Waldenstrom's Macroglobulinaemia

PRIOR TO A COURSE OF TREATMENT

- Determine performance status. Patient must have (ECOG) performance status of less than or equal to 2.

- Check full blood count. Absolute neutrophil count greater than or equal to 0.75 x 10^9/L independent of growth factor support. Platelet count of greater than or equal to 30 x 10^9/L

- Check liver function test. Reduce dose in liver impairment (see below)

- Pregnancy test for child bearing females. Fertile sexually active males and females must practice a highly effective method of birth control. These restrictions apply for one month after last dose Ibrutinib in female and three months in male. The effect on fertility is unknown

- Check HIV, hepatitis B and hepatitis C status. There is now an established risk of hepatitis B reactivation following ibrutinib use. Seek hepatology opinion in positive cases.

- Monitor patients for tumour lysis, take appropriate precautions in those patients with high tumour burden

- Written consent for course.

- Consider prophylaxis in those patients at risk of opportunistic infections. Studies have now shown a slightly increased risk of infections such as Aspergillosis and Pneumocystis Jirovecci.

- ECG to establish baseline heart rhythm.

Cautions/Contraindications

- Warfarin use / anticoagulation. Ibrutinib induces a mild bleeding diathesis

- Haemorrhagic stroke / positive bleeding history

- On-going uncontrolled active systemic infection

- Ibrutinib should be held at least 3-7 days pre and post surgery

- Severe cardiovascular disease. Cardiac arrhythmias.

- Patients taking CYP3A4/5 inhibitors should not be given ibrutinib

- Patients need to be monitored for cardiac arrhythmias in clinic. There is an increased incidence of atrial fibrillation and also ventricular tachycardia.
  Temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular tachycardia (palpitations, chest pain, dizziness or syncope)

- Administer to patients with severe renal impairment only if benefits outweigh the risks

Dose:

Ibrutinib 420mg orally once daily

Take orally daily with a glass of water approximately the same time each day
The capsule should be swallowed whole with water. Do not open, break or chew the capsules.

SIDE EFFECTS

- Diarrhoea
- Fatigue
- Upper respiratory tract infection
- Nausea
- Peripheral oedema
- Dyspnoea
- Vomiting
- Constipation
- Anorexia
- Cough
- Rash
- Abdominal pain
- Neutropenia
- Thrombocytopenia
- Anaemia
- Bleeding
- Leukostasis
- Atrial fibrillation
- Ventricular tachycardia
- Hepatitis B reactivation
- Opportunistic infections

Monitoring

Monitor weekly for the first eight weeks. Every four weeks until six months and then 12 weeks thereafter. Check full blood count, U&E's, liver function test.
Monitor heart rhythm.

DOSE MODIFICATION GUIDELINES

Dose modification for neutropenia (unless due to marrow infiltration).
Ibrutinib treatment should be withheld for any new onset or worsening grade 3 or greater neutropenia (less than 1) with infection or fever or grade 4 (less than 0.5) neutropenia. Once the symptoms of the toxicity have resolved to grade 1(>1.5) or baseline (recovery) the ibrutinib treatment may be reinitiated at the starting dose. If the toxicity recurs, reduce the dose by one capsule (140mg per day). A second dose reduction by 140mg per day may be considered as needed. If toxicities persist or recur following two dose reductions, discontinue ibrutinib.

Recommended dose modifications for these toxicities are described below:

Toxicity Occurrence	CLL Dose Modification After recovery Starting dose = 420mg daily
First	Restart at 420mg daily
Second	Restart at 280mg daily
Third	Restart at 140mg daily
Fourth	Discontinue Ibrutinib

Dose Modification for Thrombocytopenia (unless due to marrow infiltration)

Grade 4 thrombocytopenias (less than 25) withhold Ibrutinib. Once the thrombocytopenia has resolved to grade 1(>75) or baseline (recovery) Ibrutinib treatment can be reinitiated at the starting dose. If toxicity recurs, reduce dose by one capsule (140mg per day). A second dose reduction by 140mg per day may be considered as needed. If toxicity persists or recurs following two dose reductions, discontinue Ibrutinib.

Recommended Dose Modifications for thrombocytopenia are described below:

Toxicity Occurrence	**CLL Dose Modification After recovery Starting dose = 420mg daily**
First	**Restart at 420mg daily**
Second	**Restart at 280mg daily**
Third	**Restart at 140mg daily**
Fourth	**Discontinue Ibrutinib**

Consideration can be given to the use of GCSF, erythropoietin and blood transfusions.

Dose Modifications for Hepatic Impairment

Mild Liver Impairment (Child-Pugh Class A)	280mg od
Moderate Liver Impairment (Child-Pugh Class B)	140mg od
Severe Liver Impairment (Child-Pugh Class C)	Not recommended

Special Considerations:

1. Lymphocytosis compartmental shift well recognised with Ibrutinib therapy.

Upon initiation of treatment with ibrutinib, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5,000/μL) often associated with reduction of lymphadenopathy was observed in most patients (75%) with relapsed/refractory CLL/SLL. This effect has also been observed in 33% of patients in the MCL study. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings, occurs during the first few weeks (median time 1.1 weeks) of ibrutinib therapy and typically resolves within a median of 18.7 weeks, while on treatment.

2 Patients with lymphocyte count greater than 400,000 with CLL should be very closely monitored for signs of leukostasis

3 Administer supportive care including hydration and/or leukopheresis as indicated.

Pregnancy

Ibrutinib should not be used in pregnancy. It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk assessment should be made whether to discontinue breast feeding or discontinue Ibrutinib, taking into account the importance of the Ibrutinib to the mother.

Dr David Howarth
Consultant Haematologist
University Hospitals Morecambe Bay NHS Trust
October 2017