NHS
North West Coast
Strategic Clinical Networks

IBRUTINIB

INDICATION: Relapsed Mantle Cell lymphoma

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 independent of platelet support or stable platelet count of greater than or equal to 20 to 29 x 10^9/L due to documented bone marrow infiltration.

- Check U&E's. Serum creatinine less than or equal to 2 x upper limit of normal or estimated glomerular filtration rate greater than or equal to 30mls per minute.

- Check liver function test. ALT and AST less than or equal to 2.5 x upper limit of normal. Bilirubin less than or equal to 1.5 x upper limit of normal (unless bilirubin rises due to Gilbert's syndrome or of non-hepatic origin)

- 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.

- ECG to establish baseline heart rhythm.

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

- Written consent for course.

CAUTIONS / CONTRAINDICATIONS

- Patient received stem cell transplantation within the last six months

- Patient has evidence of GVHD and/or requires immunosuppressant therapy.

- Patient has had major surgery within the last four weeks or major wound that has not fully healed.

- History of HIV or active infection with hepatitis C or B.
- On-going uncontrolled active systemic infection.
- Patient has had a stroke within the last six months.
- Intracranial haemorrhage within the last six months.
- Requires anticoagulation with Warfarin or equivalent
- Patient requires treatment with a strong CYP3A inhibitor
- Patient has clinically significant cardiovascular disease such as:

  a) Uncontrolled or symptomatic arrhythmias
  b) Congestive cardiac failure
  c) Myocardial infarction within the last six months
  d) Class III or IV cardiac disease as defined by the New York Heart Association and functional classification

Dose:

Ibrutinib 560mg 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.

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)

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	MCL Dose Modification After recovery Starting dose = 560mg daily
First	Restart at 560mg daily
Second	Restart at 420mg daily
Third	Restart at 280mg daily
Fourth	Discontinue Ibrutinib

Dose Modification for Thrombocytopenia (unless due to marrow infiltration)

Grade 4 thrombocytopenia (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	**MCL Dose Modification After recovery Starting dose = 560mg daily**
First	**Restart at 560mg daily**
Second	**Restart at 420mg daily**
Third	**Restart at 280mg daily**
Fourth	**Discontinue Ibrutinib**

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

Special Considerations:

1. Lymphocytosis compartmental shift well recognised with Ibrutinib therapy.
2. Lymphocyte count recognised to increase particularly during the first two to three months of therapy followed by return to baseline over six months.
3. Lymphocyte count greater than 100,000 per MCL are at increased risk of leukostasis.
4. Patients with lymphocyte count greater than 400,000 per MCL should be very closely monitored.
5. Consider withholding ibrutinib.
6. Administer supportive care including hydration and/or leukopheresis as indicated.

Drug Interactions

Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4/5.

Concomitant use of Ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase Ibrutinib exposure and should be avoided (e.g. ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, itraconazole).

If strong CYP3A inhibitor must be used, a dose reduction of ibrutinib to 140mg daily or temporary suspension of ibrutinib should be considered. Patients should be closely monitored for signs of ibrutinib toxicity. Grapefruit juices and Seville oranges should be avoided for the duration of ibrutinib treatment as they contain moderate inhibitors of CYP3A.

Administration of ibrutinib with strong inducers of CYP3A causes a ten-fold decrease in ibrutinib exposure. Avoid use of strong CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin and St John's wort), consider alternative agents with less or no CYP3A induction. Co-administration of narrow therapeutic index Pgp substrates (e.g., digoxin) with ibrutinib may increase blood concentration and should be used with caution and patients monitored closely for toxicity.

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.

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