**Idelalisib (Zydelig®) and Rituximab for CLL**

**DRUG ADMINISTRATION SCHEDULE**

<table>
<thead>
<tr>
<th>DAY</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1, 15, 29, 43, 57 Then Weeks 12, 16 &amp; 20</td>
<td>Paracetamol</td>
<td>1 gram</td>
<td>Oral</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>100 mg</td>
<td>IV bolus</td>
<td>via 0.9% NaCl drip</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Chlorphenamine</td>
<td>10 mg</td>
<td>IV bolus</td>
<td>via 0.9% NaCl drip</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td><strong>Rituximab</strong></td>
<td></td>
<td></td>
<td></td>
<td>See below</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV infusion</td>
<td><em>250ml 0.9% NaCl</em></td>
<td>See below</td>
</tr>
<tr>
<td>Day 1</td>
<td><strong>Idelalisib</strong></td>
<td>150 mg</td>
<td>Oral</td>
<td>TWICE daily</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>Allopurinol</td>
<td>300 mg</td>
<td>Oral</td>
<td>ONCE daily</td>
<td>Review after 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Loperamide</td>
<td>2 mg</td>
<td>Oral</td>
<td>When required</td>
<td>Max 16mg/24hr</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide</td>
<td>10 mg</td>
<td>Oral</td>
<td>THREE times daily</td>
<td>As required</td>
</tr>
</tbody>
</table>

*Some centres may supply rituximab in 500ml on the first cycle to make the infusion rates easier to work with.*

**The dose of rituximab is 375mg/m^2 for the first infusion and then increased to 500mg/m^2 for all subsequent infusions**

**CYCLE LENGTH AND NUMBER OF DAYS**
- Rituximab is given every 2 weeks for 5 doses and then every 4 weeks for 3 doses, for a total of 8 infusions.
- i.e. Rituximab on week 0, week 2, week 4, week 6, week 8, week 12, week 16 & week 20
- Idelalisib should be taken continuously until progression.

**APPROVED INDICATIONS**
As per NICE TA TA359 Idelalisib, in combination with rituximab, is recommended:
- for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or
- for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months.

Idelalisib is recommended only if the company provides the drug with the discount agreed in the simple discount agreement.

**INVESTIGATIONS / MONITORING REQUIRED**

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>before every rituximab dose, then monthly for the first 6 months, then up to every 3 months in stable patients</td>
</tr>
<tr>
<td>LFTs, including transaminases</td>
<td>every 2 weeks for 3 months, then as clinically indicated</td>
</tr>
<tr>
<td>U&amp;Es</td>
<td>every 4 weeks</td>
</tr>
<tr>
<td>LDH</td>
<td>every 8 weeks</td>
</tr>
</tbody>
</table>
RECOMMENDED TAKE HOME MEDICATION

Antiemetic’s not routinely required.
Consider PCP propylaxis with Idelalisib, Aciclovir 400mg twice daily and co-trimoxazole 960mg three times per week.

ASSESSMENT OF RESPONSE

Haematological response
Palpable disease
B symptoms

REVIEW BY CLINICIAN

To be reviewed by either a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW

On cycles where not seen by clinician.

ADMINISTRATION NOTES

- Patients receiving rituximab must be screened for Hepatitis B prior to starting treatment.
- Biosimilar intravenous rituximab is now available and used a standard All of the information in this protocol applies the biosimilar brands of rituximab.
- Risk of hypersensitivity and anaphylaxis with Rituximab – particularly during the first cycle for the first two hours of administration. Monitor patient every 15 minutes for first hour then every 30 minutes. Symptoms usually resolve with interruption of rituximab and administration of antipyretic and antihistamines. Some patients will require oxygen, intravenous fluids (0.9% Sodium Chloride), bronchodilators (e.g. nebulised salbutamol), and glucocorticoids (e.g. IV hydrocortisone).
- Risk of severe hypersensitivity (cytokine release syndrome) increases when Peripheral Lymphocytes > 25 cells x10^9/l – treatment should only proceed with caution in this setting. Reducing the infusion rate, using a different therapy first line or splitting the dose over two days (100mg on day 1, with the balance of the dose on day 2, i.e. 375mg/m^2 – 100mg) may be appropriate.
- Idelalisib is available as 100mg and 150mg tablets. The tablets should be swallowed whole, either with or without food.
- Avoid co-administration with CYP3A inducers (e.g. rifampicin, phenytoin, St John’s wort, carbamazepine) as this may result in reduced plasma concentrations of Idelalisib.
- The primary metabolite of Idelalisib is a strong CYP3A4 inhibitor, and so the concomitant use of Idelalisib with medicinal products metabolised by the CYP3A4 may lead to increased serum concentrations of the other product. When Idelalisib is co-administered with other medicinal products, the Summary of Product Characteristics (SPC) for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.
- Concomitant treatment of Idelalisib with CYP3A substrates with serious and/or life-threatening adverse reactions (e.g. alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam and triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.
Rituximab Infusion Rates:

- First cycle of rituximab should commence at 50mg/hour and increase in rate by 50mg/hour every 30 minutes (to a maximum of 400mg/hour) provided the patient does not develop any signs of infusion reaction. Subsequent cycles (provided the previous cycle has been tolerated well) can start at 100mg/hour and increase by 100mg/hour every 30 minutes to a maximum of 400mg/hour. The infusion rate can be calculated by:

\[
\text{Infusion Rate [ml/hour]} = \frac{\text{Infusion Volume [ml]} \times \text{Rate [mg/hour]}}{\text{Total Dose [mg]}}
\]

- Blood Pressure, Pulse and Respiration rate should be measured every 15 minutes for the first hour of infusion, and then every 30 minutes subsequently.

- Rapid Infusion: a few small studies have demonstrated that it is possible to give rituximab at a faster rate for the second or third cycle. This practice is unlicensed and clinicians wishing to follow this practice should check with their own trust prior to adopting this practice. The unlicensed nature of the infusion rate should be explained to patients at the time of consent.

- The rapid infusion rate used is 20% of the dose over 30 minutes (100ml/hour), followed by the remaining 80% over just 60 minutes (200ml/hour). Rapid infusion should only be considered for patients who have shown no signs of adverse reaction during previous infusions, and is contra-indicated in patients.

**TOXICITIES**

**Rituximab**: severe cytokine release syndrome – usually occurs within 1 – 2 hours of the first rituximab infusion and consists of fever, headache, rigors, flushing, nausea, rash, URTI symptoms; increased risk of infections; tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration); transient hypotension and bronchospasm are usually infusion rate related.

**Idelalisib**: increased transaminases; diarrhoea; pneumonitis; rash

**DOSE MODIFICATION / TREATMENT DELAYS**

**Haematological Toxicity:**

If counts become low during treatment, this may be due to marrow infiltration and should be discussed with the consultant before any further treatment is given.

**Elevated liver transaminases:**

<table>
<thead>
<tr>
<th>ALT / AST</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 – 5 x ULN</td>
<td>Increase monitoring of LFTs, including AST, to every week until the values fall to &lt;3 x ULN</td>
</tr>
<tr>
<td>First occurrence of &gt;5 x ULN</td>
<td>Withhold Idelalisib until ALT/AST &lt;3 x ULN. Then re-start Idelalisib treatment at 100mg twice daily. If this event does not recur at 100mg bd, the dose can be increased to 150mg twice daily again, at the discretion of the consultant</td>
</tr>
<tr>
<td>Second occurrence of &gt;5 x ULN</td>
<td>Withhold Idelalisib until ALT/AST &lt;3 x ULN. Re-initiation at 100mg twice daily may be considered, at the direction of the consultant</td>
</tr>
</tbody>
</table>
Diarrhoea/colitis:
Idelalisib must be withheld in the event of grade 3 or 4 diarrhoea/colitis. Once diarrhoea/colitis has returned to ≤ Grade 1, Idelalisib can be resumed at 100 mg bd. If diarrhoea/colitis does not recur, the dose can be re-escalated to 150 mg bd, at the discretion of the Consultant.

Pneumonitis:
- Idelalisib must be withheld in the event of suspected pneumonitis, and the patient treated accordingly. Once pneumonitis has resolved and if re-treatment is considered appropriate, resume at 100 mg bd.
- Treatment must be discontinued for moderate or severe symptomatic pneumonitis.

Rash:
Idelalisib must be withheld in the event of Grade 3 or 4 rash. Once rash has returned to ≤ Grade 1, treatment can be resumed at 100 mg bd. If rash does not recur, the dose can be re-escalated to 150 mg twice daily, at the discretion of the Consultant.

Renal Impairment:
No idelalisib dose adjustments are required for patients with mild, moderate or severe renal impairment.

Hepatic Impairment:
- No dose adjustment of idelalisib is required when initiating treatment in patients with mild or moderate hepatic impairment, but an intensified monitoring of adverse reactions is recommended, as drug exposure is expected to be increased.
- There is insufficient data to make dose recommendations for patients with severe hepatic impairment. Therefore, caution and extra monitoring is recommended if using idelalisib in this population.

TREATMENT LOCATION
Can be given at Cancer units

REFERENCES:
1. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia; Furman, R et al; NEJM 2014; 370: 997 – 1007
2. Idelalisib for treating chronic lymphocytic leukaemia. NICE technology appraisal guidance TA359 Published date: October 2015