Chemotherapy Protocol

Mantle Cell Lymphoma

Ibrutinib

Regimen

- MCL – Ibrutinib (560mg)

Indication

- Mantle Cell Lymphoma with cyclin D1 overexpression or translocation breakpoints at 
  t (11;14)

- Failure to achieve at least a partial response (PR) with, or documented disease 
  progression disease after, the most recent treatment regimen

- At least one but no more than five previous lines of treatment

- WHO performance status 0, 1, 2

Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>Diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising,</td>
</tr>
<tr>
<td></td>
<td>rash, nausea, pyrexia, neutropenia, thrombocytopenia, constipation, atrial</td>
</tr>
<tr>
<td></td>
<td>fibrillation, ventricular tachycardia, hypertension, onycholclasis</td>
</tr>
</tbody>
</table>

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of 
Product Characteristics for full details.

Monitoring

- FBC, U&Es and LFTs prior to starting treatment and then every twenty-eight days for 
  the first twelve weeks of treatment. Thereafter if counts are stable monitoring may 
  take place every twelve weeks.

- Hepatitis B status prior to starting treatment as re-activation is a known adverse 
  effect of treatment

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug 
specific toxicities only. Dose adjustments may be necessary for other toxicities as well.
Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

**Haematological**

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if the patient is symptomatic of anaemia or where the haemoglobin is less than 8g/dL (80g/L).

Dose delay if neutrophils are less than $1 \times 10^9/L$ with infection or fever or the neutrophils are less than $0.5 \times 10^9/L$ or the platelets are less than $30 \times 10^9/L$. Restart treatment once the toxicity has resolved to grade 1 using the dosing table below.

<table>
<thead>
<tr>
<th>Toxicity Occurrence</th>
<th>Dose Modification after Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Re-start at 560 mg once a day</td>
</tr>
<tr>
<td>Second</td>
<td>Re-start at 420 mg once a day</td>
</tr>
<tr>
<td>Third</td>
<td>Re-start at 280 mg once a day</td>
</tr>
<tr>
<td>Fourth</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

Ibrutinib is metabolized in the liver. When using ibrutinib in patients with mild or moderate hepatic impairment, monitor patients for signs of toxicity and follow dose modification guidance as needed.

<table>
<thead>
<tr>
<th>Liver Function</th>
<th>Ibrutinib Dose Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child Pugh A (mild hepatic impairment)</td>
<td>280mg once a day</td>
</tr>
<tr>
<td>Child Pugh B (moderate hepatic impairment)</td>
<td>140mg once a day</td>
</tr>
<tr>
<td>Child Pugh C (severe hepatic impairment)</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Renal Impairment**

No dose adjustments are required for patients with a creatinine clearance of more than 30ml/minute. There are no data in patients with a creatinine clearance of less than 30ml/min or patients on dialysis. In this latter instance prescribed ibrutinib only if the benefit outweighs the risk, monitor patients carefully for signs of toxicity.

**Other Toxicity**

Dose delay for any new onset or worsening grade non-haematological toxicity as described in the table below. Restart treatment once the toxicity has resolved to NCI-CTC grade 1 or below using the table below.

<table>
<thead>
<tr>
<th>NCI-CTC Grade</th>
<th>Ibrutinib Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1, 2</td>
<td>No change</td>
</tr>
<tr>
<td>3 or more</td>
<td>Withhold, restart once the toxicity has resolved to grade 1 using the dosing table shown above</td>
</tr>
</tbody>
</table>
Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in Aria)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>560mg</td>
<td>1- 28 (inclusive)</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Dose Information

- Ibrutinib is available as 140mg, 280mg, 420mg and 560mg tablets.
- The dose will be rounded to the nearest 140mg (up if halfway).

Administration Information

- Ibrutinib tablets should be swallowed whole with water at approximately the same time each day.

Additional Therapy

- Anti-infective prophylaxis with
  - co-trimoxazole 960mg once day on Monday, Wednesday and Friday oral

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to ibrutinib.
- It must be made clear to all staff, including those in the community, that ibrutinib is should only be prescribed under the supervision of a consultant haematologist or oncologist.
- There are many drug interactions associated with ibrutinib. Caution is advised when concurrently prescribing agents that affect coagulation or platelet function or that influence the hepatic enzyme system CYP3A4.
- 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.
- Grapefruit and grapefruit juice, and Seville oranges, should be avoided while on ibrutinib

Coding

- Procurement – X71.5
- Delivery – X73.1

References

REGIMEN SUMMARY

Ibrutinib (560mg)

Cycle 1 onwards

Day 1-28 inclusive

1. Ibrutinib 560mg once a day oral
   Administration Information
   Oral Chemotherapy
   
   Ibrutinib tablets should be swallowed whole with water at approximately the same time each day.

   Avoid grapefruit and grapefruit juice, and Seville oranges while on ibrutinib. Always check for drug interactions.

2. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
   Administration Instructions
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice. Please dispense 28 days.
This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts:

- Hampshire Hospitals NHS Foundation Trust
- NHS Isle of Wight
- Portsmouth Hospitals NHS Trust
- Salisbury NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Written By</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>October 2019</td>
<td>Ibrutinib capsules changed to tablets</td>
<td>Nanda Basker Pharmacist</td>
<td>Dr Deborah Wright Pharmacist</td>
</tr>
<tr>
<td>1.2</td>
<td>February 2018</td>
<td>Co-trimoxazole added as supportive therapy. Grapefruit interaction moved to additional information section. Some re-formatting in tables</td>
<td>Dr Deborah Wright Pharmacist</td>
<td>Dr Rob Lown Consultant Haematologist</td>
</tr>
</tbody>
</table>
| 1.1     | September 2017 | Ventricular tachycardia added to adverse effects
Hepatitis B status added to monitoring                                  | Dr Deborah Wright Pharmacist | Rebecca Wills Pharmacist    |
| 1       | February 2017 | None                                                                      | Dr Deborah Wright Pharmacist | Dr Helen Dignam Consultant Haematologist |