GUIDELINES ON THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA

INVESTIGATIONS
1. Define stage of disease (see table)
2. Document percentage of blasts, basophils & eosinophils in peripheral blood.
3. Spleen size (cm below costal margin)
4. Bone Marrow for FISH and karyotype. (peripheral blood FISH may be sufficient in some patients)
5. Peripheral blood for BCR-ABL transcript baseline (PCR)

INITIAL MANAGEMENT
1. Consider leucopheresis for symptomatic hyperleucocytosis
2. Consider entry into SPIRIT trial: www.spirit-cml.org
3. For non-trial patients Imatinib 400 mg (CP), 600 mg (AP/BC)
4. Hydroxycarbamide may be appropriate if patient has short life expectancy due to co-morbidities
5. Hydroxycarbamide not usually required prior to Imatinib but may be used whilst definitive diagnosis awaited.

TOXICITY MONITORING
1. FBC (10-15% early neutropenia and thrombocytopenia)
   Stop Imatinib if platelets <50 or neutrophils <1.0
   Consider GCSF to maintain dose 300-400 mg as much as possible
2. LFTs (occasional patients develop late liver toxicity 1-2 yrs+ out)
3. Potentially teratogenic – advise contraception
4. Side-effects: nausea, diarrhoea, oedema, myalgia, headache, rash, cardiac failure (rare)
5. Drug interactions: Manufacturer recommends use of heparin rather than warfarin.
   Imatinib increases plasma concentration of simvastatin.
   Few other common drug interactions (see Appendix 1, BNF)

MONITORING DISEASE RESPONSE
1. BM or Peripheral blood for FISH 3-6 monthly until <0% (CCR)
2. Thereafter 3 monthly Peripheral blood for BCR/ABL ratio by PCR
   Aim for Major Molecular Response (ratio <=0.1%)
3. Reduce to 6 monthly PCR once in MMR for more than 2 years
4. Consider bone marrow karyotyping yearly (not essential if MMR )

PHASE OF DISEASE

<table>
<thead>
<tr>
<th></th>
<th>Accelerated Phase</th>
<th>Blast Phase/Crisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Phase</td>
<td>Blast cells 15-29% in PB/BM</td>
<td>Blast cells &gt;/=30% in PB or BM</td>
</tr>
<tr>
<td>No features of AP or BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional cytogenetic abnormalities alone do not indicate accelerated phase</td>
<td>Blast cells + Promyelocytes &gt;30% in PB/BM but Blasts &lt;30%</td>
<td>Extramedullary blast involvement</td>
</tr>
<tr>
<td>Basophils &gt;20% in PB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DEFINITIONS OF RESPONSE

Please note: The following table is based on the Baccarani Leukaemia Net Guidelines of 2006. The percentages of Ph+ cells quoted in these guidelines are for bone marrow examination. For most CML patients the TVCN Leukaemia Group suggest routine monitoring of peripheral blood with bone marrow examination as appropriate at critical points, especially in patients who are not responding optimally to therapy. It is therefore suggested that clinicians exert appropriate judgement as to the correct combination of monitoring of blood versus marrow monitoring.

<table>
<thead>
<tr>
<th>Time on Imatinib</th>
<th>Failure of Response</th>
<th>Suboptimal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>No Haem Response</td>
<td>Ph+ &gt;35% (~50% achieve CCR by 2 yrs)</td>
</tr>
<tr>
<td>6 months</td>
<td>No Complete Haem Response* or Ph+ &gt;95%</td>
<td>Ph+ &gt;/=1% (no CCR)</td>
</tr>
<tr>
<td>12 months</td>
<td>Ph+ &gt;35%</td>
<td>Ph+ &gt;/=1% (no CCR)</td>
</tr>
<tr>
<td>18 months</td>
<td>Ph+ &gt;/=1% (no CCR)</td>
<td>BCR/ABL ratio &gt; 0.1 (no MMR)</td>
</tr>
<tr>
<td>Anytime</td>
<td>Loss of CCR</td>
<td>Loss of MMR or Additional chromosomal abnormalities</td>
</tr>
</tbody>
</table>

*CHR = platelets <450, WBC <10, no myelocytes on PB, <5% basophils

IF SUBOPTIMAL RESPONSE

1. Confirm no improvement over a 6 month period
2. Consider Bone Marrow for karyotype and mutation analysis (d/w Dr Schuh)
3. Consider Imatinib serum levels
4. Consider dose increase (could discuss at MDT)
5. Continue 3 monthly monitoring

IF FAILING THERAPY

1. Repeat to confirm
2. Bone marrow for karyotype
3. Bone marrow for mutation analysis if available – d/w Dr Schuh (e.g. T315I mutation resistant to Dasatinib and Nilotinib)
4. Consider Imatinib serum levels
5. Tissue Type siblings if suitable allograft recipient
6. Consider increased dose or change to alternative Tyrosine Kinase Inhibitor (Dasatinib or Nilotinib)
7. Consider Hydroxymercormide if these approaches fail or are not suitable
8. Discuss at MDT

REFERENCES