Clinical Guidelines for Leukaemia and other Myeloid Disorders – Myeloproliferative Neoplasms

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Insert names of authors of the section: Dr Sebastian Francis
Version History

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<th>Date Issued</th>
<th>Brief Summary of amendments</th>
<th>Owner’s Name:</th>
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<td>Dr</td>
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(Please note that if there is insufficient space on this page to show all versions, it is only necessary to show the previous 2 versions)

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OUTLINE MANAGEMENT FOR PH+VE CHRONIC MYELOID LEUKAEMIA

Definitions of disease:

WHO Criteria for Chronic Phase
- None of the features of accelerated phase or blast crisis (BC)

WHO criteria for Accelerated Phase:
- Blasts in blood or bone marrow 10-19%
- Basophils of more than 20%
- Thrombocytopenia: persistent and unrelated to therapy (<100)
- Thrombocytosis >1000 and unresponsive to therapy
- Cytogenetic evidence of clonal evolution (i.e. abnormalities not present at diagnosis).

Criteria for Blast Crisis
- WHO criteria blast cells in peripheral blood or bone marrow >20%
- Extramedullary blast proliferation, or large foci or clusters of blasts in the bone marrow biopsy.

Investigations at Diagnosis

All diagnostic samples should be sent to the HODS lab for appropriate investigation.

Diagnostic samples:

Morphology
Peripheral blood film
Diagnostic Bone Marrow (if blood film morphology equivocal)
- Aspirate
- Trephine

Cytogenetics
Peripheral blood sample (Lithium Heparin) or bone marrow aspirate sample for G-Banding cytogenetics and FISH for bcr-abl

Molecular genetics
EDTA peripheral blood sample x2
  a. Characterization of bcr-abl fusion breakpoint
  b. Q-PCR for baseline level of bcr-abl/abl ratio

Tissue typing
Consider tissue typing patients with clonal chromosomal aberrations (trisomy 8, double Philadelphia positive, isochromosome 17, trisomy 19, ider (22)(q10)t(9;22)(q34;q11) if less than 65 years.

Prognostic scoring systems

Sokal score (low/intermediate/high)
EUTOS score

Treatment

Imatinib 400mg (hydroxycarbamide may be used initially to control WCC if exceedingly high) for chronic phase disease (NICE guidance). Nilotinib 300mg bd can also be used but no survival benefit demonstrated.

Consider Nilotinib in newly diagnosed females of childbearing age (nilotinib achieves deeper responses faster (Can therefore be stopped prior to attempting pregnancy).

Therapeutic leucopheresis can be considered if there is priapism or deteriorating Glasgow Coma Scale at initial presentation.

*Test patients for infection with hepatitis B virus (HBV) before starting treatment with BCR-ABL tyrosine kinase inhibitors. Consult experts in liver disease and in the treatment of HBV before starting treatment with BCR-ABL tyrosine kinase inhibitors in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV during treatment. Patients who are carriers of HBV who require treatment with BCR-ABL tyrosine kinase inhibitors should be closely monitored for signs and symptoms of active HBV infection throughout treatment and for several months after stopping.

Definitions of response to therapy

Complete Haematological Response
  - Platelets <450
  - WCC <10
  - Differential showing no immature granulocytes and <5% basophils
  - Non palpable spleen

Cytogenetic response (FISH on PB cells can be used instead of BM)
  - *Complete 0% Ph+ve cells (>20 marrow metaphases)
  - Partial 1-35%
  - Minor 36-65%
  - Minimal 66-95%
  - None >95%
*Patients who achieve complete cytogenetic response should have their ongoing response to therapy monitored by serial bcr-abl/abl ratio testing.
Molecular Response
- Complete - Bcr-abl not-detectable
- Major <0.1% (i.e. >3 log reduction in bcr-abl/abl ratio).

Loss of response
- Loss of CCR
- Rising BCRABL of 0.5 log on 2 occasions

Monitoring Therapy

At diagnosis:
- Chromosome banding analysis (CBA) of marrow cell metaphases in at least 20 metaphases analysed.
- FISH in case of Ph-(for cryptic or variant translocation)
- Qualitative PCR(transcript type)

During treatment:
- RQ-PCR every 3 months until MMR has been achieved and then every 3-6 months
- +/- Bone marrow aspirate for (CBA) every 3, 6 and 12 months until CCR has been achieved, then every 12 months

Failure, Progression:
- RQ-PCR, mutational analysis, and CBA.

Mutation analysis:
- Failure to achieve milestones, rising bcrabl or loss of CCR

Response definitions for TKI (as per ELN criteria)

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal response</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>High risk</td>
<td>Major route CCA/Ph+</td>
</tr>
<tr>
<td>3 mos.</td>
<td>BCR-ABL &lt;10%* Ph+ ≤35% (PCyR)</td>
<td>BCR-ABL &gt;10%* Ph+ 36-95%</td>
<td>No CHR* Ph+ &gt;95%</td>
</tr>
<tr>
<td>6 mos.</td>
<td>BCR-ABL &lt;1%* Ph+ 0% (CCyR)</td>
<td>BCR-ABL 1-10%* Ph+ 1-35%</td>
<td>BCR-ABL &gt;10%* Ph+ &gt;35%</td>
</tr>
<tr>
<td>12 mos.</td>
<td>BCR-ABL ≤0.1% (MMR)</td>
<td>BCR-ABL 0.1-1%* Ph+ &gt;0%</td>
<td>BCR-ABL &gt;1%* Ph+</td>
</tr>
<tr>
<td>Then, and at any time</td>
<td>MMR or better</td>
<td>CCA/Ph- (-7, or 7q-)</td>
<td>Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+</td>
</tr>
</tbody>
</table>
Key Points

Failure to achieve milestones at particular time points requires MDM review for advice on alternative TKI

Try to maintain dose >300mg/day, gcsf may be required

<table>
<thead>
<tr>
<th>Response at 12 months</th>
<th>% of progression free survival at 42 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CCyR</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;3 log reduction (CCyR)</td>
<td>90%</td>
</tr>
<tr>
<td>&gt;3 log reduction (MMR)</td>
<td>98%</td>
</tr>
</tbody>
</table>

IRIS Study – the achievement of >3 log reduction (MMR) months predicts progression free survival and duration of CCyR.

Criteria for consideration BMT opinion.
- Patients failing imatinib and another TKI (resistance)
- Patients intolerant of at least 2 TKI

Indications for second generation TK inhibitors
- Patients intolerant to Imatinib
- Patients who fail/resistant to Imatinib therapy
- The European LeukaemiaNet definition of Imatinib failure in chronic phase CML

After Imatinib failure try nilotinib 400mg bd (2 hour fast). Ensure cardiovascular risk factors are addressed. All patients require a kinase domain mutation analysis prior to starting nilotinib. If patient <65 then consider referral for allograft discussion if haematological toxicity with imatinib.

Patients failing imatinib have approximately 40-50% of achieving CCR on nilotinib. There is evidence that third line therapy using 2nd generation TKI can achieve a response in 30% of patients. However, if cytopenias are a significant problem, a
state that probably reflects inadequate normal stem cells, then third line therapy is unlikely to be better tolerated (Abruzzese E et al, 2008; Quintas-Cardama A et al, 2007).

**Management of CML after second generation TKI Failure**

The Hammersmith group has produced a scoring system that helps to identify patients unlikely to respond to 2G-TKI before their initiation.

Low risk scores = reasonable to commence Nilotinib / Dasatinib irrespective of transplant risk

High risk scores = use EBMT pre transplant risk assessment score

**Table**

*Pre-second-generation tyrosine kinase inhibitor (2G-TKI) score*

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal risk group</td>
<td>Low</td>
<td>Intermediate or high</td>
</tr>
<tr>
<td>Neutropenia during Imatinib therapy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Institution of 2G-TKI&gt;18 months after Imatinib failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Best cytogenetics response on Imatinib (% Ph-positive cells)</td>
<td>&lt;95%</td>
<td>&gt;95%</td>
</tr>
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</table>

**The three-year cumulative incidence of complete cytogenetics remission (p<0.0001)**

<table>
<thead>
<tr>
<th>Score</th>
<th>0-1</th>
<th>2</th>
<th>3-4</th>
</tr>
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<tbody>
<tr>
<td>Complete cytogenetic remission</td>
<td>95.6%</td>
<td>50%</td>
<td>18.7%</td>
</tr>
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</table>

**CDF Criteria**

**Dasatinib**

- If a patient is refractory/intolerant to imatinib (grade 3 or 4) and intolerant to nilotinib (grade 3 or 4) and in chronic phase
- Accelerated phase CML where patient is refractory or significant intolerance to imatinib (grade 3 or 4) and intolerant to nilotinib

Need to monitor for pleural/pericardial effusions.

**Bosutinib**

- Intolerance to nilotinib and dasatinib (grade 3 or 4) and in chronic phase

**Ponatinib**

- Patients with T513I mutation

**Relevance of BCR-ABL kinase domain mutations**
Advanced phase patients:-

Mutations should be sought in any patient presenting in advanced phase disease. The search could be repeated in such cases if they fail to achieve a response to a TK inhibitor or if having responded subsequently has a rise in the number of BCR-ABL transcripts.

If patient has T315I then requires ponatinib as per the CDF.

**Management of intolerance to Imatinib**

Intolerance must be considered on a patient to patient basis.
Supportive care and side effect management should be employed
If the patient is truly intolerant (grade3/4), options that may be considered include:-
- Second generation TK inhibitor Nilotinib, followed by Dasatinib (as per CDF)

**Pregnancy**

Women of child bearing age who have not completed their family should consider nilotinib treatment as first line treatment.
The rational for this is a fast and deep response can be achieved. Once achieved a stable MMR for at least 2 years then stop TKI to allow for conception. Patients will require regular fbc and bcrabl monitoring. If wcc rises then start interferon.
Breast feeding is contraindicated while on TKI therapy.

References

GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF POLYCYthaEMIA VERA

Diagnosis
All patients with a persistently raised venous haematocrit (Hct) (>0.52 males; >0.48 females for >2 months) should have a red cell mass (RCM). Males and females with Hct values above 0.60 and 0.56 respectively can be assumed to have an absolute erythrocytosis and do not require confirmatory studies.

The following diagnostic criteria should be used:-
(based on Campbell & Green, 2006)

**JAK2-positive polycythaemia vera**

A1 High haematocrit (>0.52 in men; >0.48 in women) OR raised red cell mass (>25% above predicted)
A2 Mutation in JAK2/Jak2 exon 12

Diagnosis requires both criteria to be present.

**JAK2-negative polycythaemia vera**

Major
A1 Raised red cell mass (>25% above mean normal predicted value) or Hct > 0.60 males; > 0.56 females)
A2 Absence of mutation in JAK2
A3 No cause for secondary erythrocytosis (Normal arterial oxygen saturation and no elevation in EPO)
A4 Palpable splenomegaly
A5 Presence of acquired genetic abnormality (excluding BCR-ABL).

Minor
B1 Thrombocytosis (platelet count > 450 x 10^9/l).
B2 Neutrophil leucocytosis (neutrophil count > 10 x 10^9/l in non-smokers; >12.5 x 10^9/l in smokers).
B3 Splenomegaly (demonstrated on isotope/ultrasound scanning)
B4 Characteristic BFU-E growth or low serum erythropoietin.

Diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Management

**Primary care:**
Address risk factors such as DM, Hypertension and Hyperlipidaemia

**Venessection:**
The Hct should be maintained at less than 0.45 by venesection. The volume removed should be commensurate with the patient’s size and comorbidities.

**Aspirin:**
75mg/day unless it is contraindicated

**Cytoreduction** (should be considered if):
- Poor tolerance of venesection
- Symptomatic or progressive splenomegaly
- Other evidence of disease progression e.g. weight loss, night sweats, fevers
- Thrombocytosis

**Choice of therapy:**
- **< 40 years:** 1st line Interferon
  2nd line hydroxycarbamide or anagrelide
- **40-75 years** 1st line Hydroxycarbamide
  2nd line interferon or anagrelide
- **>70 years** 1st line Hydroxycarbamide
  2nd line 32P or i/m low dose busulphan
DIAGNOSIS AND MANAGEMENT OF ESSENTIAL THROMBOCYTHAEMIA

Diagnostic Criteria
(based on BCSH, 2015) Diagnosis requires A1-A3 OR A1 + A3-A5

JAK2-positive thrombocythaemia

A1 Platelet count >450
A2 Presence of an acquired pathogenetic mutation (eg in the JAK2 or CALR genes +CMPL)
A3 No other myeloid malignancy, especially PV1, PMF2, CML3, MDS4
A4 No reactive cause for thrombocytosis and normal iron stores
A5 Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm. Reticulin is generally not increased

1-Excluded by a normal haematocrit in an iron replete patient
2-Indicated by significant marrow bone marrow fibrosis and palpable splenomegaly, blood film abnormalities or unexplained anaemia
3-Excluded by absence of BCRABL1 from marrow or PB
4-Excluded by absence of dysplasia on examination of blood film and bone marrow aspirate

Risk Stratification
Once the diagnosis is established then the patient risk group should be determined as follows:

Low-risk:
(Patients having all of the following features)

• Age < 40 years
• Platelet count less than 1500[^9]/l
• No history of ischaemia, thrombosis or embolic features or erythromelalgia
• Absence of haemorrhage considered related to ET
• Absence of diabetes
• Absence of hypertension

Intermediate risk:
(Patients having all of the following features)

• Age 40-59 years
• Platelet count <1500[^9]/l
• No history of ischaemia, thrombosis or embolic features or erythromelalgia
• Absence of haemorrhage considered related to ET
• Absence of diabetes
• Absence of hypertension
High risk:
(Patients having any of the following features)
- Age > 60 years
- Platelet count > 1500\(^9\)/l
- History of ischaemia, thrombosis or embolic features or erythromelagia
- Haemorrhage considered related to ET
- Presence of diabetes
- Presence of hypertension

Treatment options
Assess and optimise other vascular risk factors such as smoking, DM, HTN.

Low/Intermediate risk disease:
- Aspirin only
- Manage vascular risk factors
- Cytoreductive therapy only if symptomatic (splenomegaly, erythromelagia), severe microvascular symptoms not improving with aspirin, uncontrolled bleeding associated with high platelets

High Risk Disease:
1\(^{st}\) line Hydroxycarbamide (interferon in patients <40)
2\(^{nd}\) line Anagrelide (Bone marrow trephine every 3 years while on anagrelide to monitor MF transformation). Other agents to consider are interferon, busulphan and P32 (busulphan/p32 only in patients>70). Consider relaxing platelet target to 400-600 in patients intolerant/resistant to Hydroxycarbamide.

Failure of hydroxycarbamide is defined as follows:-
(LeukaemiaNet definition of clinical resistance/intolerance to hydroxycarbamide in ET)
Platelet count > 600,000/ul after 3 months of at least 2g/day of hydroxycarbamide (2.5g/day in patients with body weight > 80kg).

Or
WBC <2500/ul and platelet count between 400,000/ul and 600,000/ul, or WBC <3000 and platelet count >600,000 ay any dose of hydroxycarbamide

Or
Hb <10g/dl and platelet count >400,000/ul at any dose of hydroxycarbamide

Or
Presence of leg ulcers or other unacceptable muco-cutaneous manifestation at any dose of hydroxycarbamide

Or
Hydroxycarbamide- related fever
Pregnancy and ET

- All patients should be managed by a multidisciplinary team
- Therapeutic strategies in pregnancy and ET are influenced by patients’ disease status and prior obstetric history
- Pregnancy is likely to be high risk if one or more factors listed below are present. High risk pregnancies in ET should be considered for LMWH and IFN-a from the outset or during pregnancy

- Previous venous or arterial thrombosis in mother (whether pregnant or not);
- Previous haemorrhage attributed to ET (whether pregnant or not);
- Previous pregnancy complication that may have been caused by ET; e.g. unexplained recurrent first trimester loss (three unexplained first trimester losses)
- Intrauterine growth restriction (birthweight <5th centile for gestation)
- Intrauterine death or still birth (with no obvious other cause, evidence of placental dysfunction and growth restricted fetus);
- Severe pre-eclampsia (necessitating preterm delivery <34 weeks) or development of any such complication in the index pregnancy;
- Placental abruption
- Significant ante- or postpartum haemorrhage (requiring red cell transfusion);
- Marked sustained rise in platelet count rising to above $1500 \times 10^9/l$. 
Algorithm for pregnancy management in ET (as per BCSH 2010)

**ALL Patients**
- ET specific therapy
- Low dose aspirin

**On-going assessment of thrombotic risk**
- Use GECS and LMWH if appropriate

**Fetal monitoring**
- Uterine artery dopplers at 20 weeks
- Repeat at 24 weeks if bilateral notches escalate to high risk

**Labour**
- Avoid dehydration
- Potential risk of haemorrhage

**Puerperium**
- Continue ET therapy including aspirin
- 6 weeks LMWH – all patients

**PRECONCEPTION PLAN**
- Assess risk (Table VI)
- Optimize and adjust therapy

**ALL PATIENTS**

**HIGH RISK PATIENTS**

**HIGH RISK PATIENTS (Table VI) IN ADDITION**
- ET specific therapy
- Interferon alpha
- Consider LMWH if adverse previous
- Pregnancy or thrombosis

**Fetal monitoring**
- Regular fetal growth scans

**Labour**
- Adhere to local protocols for timing of LMWH and interventions

**Breastfeeding**
- Individual discussion if taking interferon
GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF IDIOPATHIC MYELOFIBROSIS

Diagnostic Criteria (BCSH 2015)

Diagnosis requires A1 + A2 and any two B criteria

A1  Bone marrow fibrosis ≥3 (on 0–4 scale)
A2  Pathogenetic mutation (e.g. in JAK2, CALR or MPL), or absence of both BCR-ABL1 and reactive causes of bone marrow fibrosis
B1  Falciform splenomegaly
B2  Unexplained anaemia
B3  Leuco-erythroblastosis
B4  Tear-drop red cells
B5  Constitutional symptoms
B6  Histological evidence of extramedullary haematopoesis

* Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37.5°C) or diffuse bone pains.

- If Jak2 negative check for CALR/MPL
- BCRABL should be checked in atypical trephines or if Jak2, c-mpl and CALR are negative
- PDGFRA/B should be excluded if significant eosinophilia present
Prognostic Factors

Therapeutic decisions on MF should be based on DIPSS Plus score. DIPSS and DIPSS plus score can be used in post-PRV and post-ET.

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPSS</th>
<th>DIPSS</th>
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</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Haemoglobin &lt;100 g/l</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Leucocyte count &gt; 25 x 10⁹/l</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Circulating blasts ≥ 1%</td>
<td>✓</td>
<td>✓</td>
</tr>
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</table>

1 point each

DIPSS-Plus: add 1 point to the DIPSS RISK GROUP* (low = 0; intermediate 1 = 1, intermediate 2 = 2 and high risk = 3) in addition for:

- Platelet count <100 x 10⁹/l
- RBC transfusion need
- Unfavourable karyotype: +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, 11q23 rearrangement

<table>
<thead>
<tr>
<th>Risk group</th>
<th>IPSS</th>
<th>Median survival (years)</th>
<th>DIPSS</th>
<th>Median survival (years)</th>
<th>DIPSS-Plus</th>
<th>Median survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>11.3</td>
<td>0</td>
<td>Not reached</td>
<td>0</td>
<td>15.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1</td>
<td>7.9</td>
<td>1 or 2</td>
<td>14.2</td>
<td>1</td>
<td>6.5</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>2</td>
<td>4.0</td>
<td>4</td>
<td>2-3</td>
<td>2-3</td>
<td>2-9</td>
</tr>
<tr>
<td>High ≥3</td>
<td>2-3</td>
<td>2-3</td>
<td>5 or 6</td>
<td>1-5</td>
<td>≥ 4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Note that this is the risk group NOT the sum of points.

Treatment

Anaemia
- EPO Injections if inadequate EPO levels (<125mU/ml)
- If after 3 months no response following increased EPO dose then consider Danazol (In males check PSA and exclude prostate ca prior to starting danazol. Require annual u/s liver)
- Thalidomide/prednisolone

Low risk
- Watch and wait.
- Interferon if symptomatic
- Hydroxycarbamide for cytoreduction

Intermediate /High risk
- Patients with symptomatic splenomegaly +/- constitutional symptoms in primary myelofibrosis, post ET myelofibrosis or post essential thrombocythaemia myelofibrosis are eligible for Ruxolitinib (if platelets>50).
- For objective monitoring of symptoms while on Ruxolitinib suggest using MPN-SAF
Allograft candidates (as per EBMT/ELN IWG)

- INT-2/High risk disease according to DIPSS or DIPSS plus and age<70 should be considered potential candidates
- INT-1 and age <65 should be considered candidates for allogeneic-SCT if they present either refractory, transfusion dependent anaemia or adverse cytogenetics (as defined by DIPSS+)

References


BCSH Guidelines 2012: Guideline for the diagnosis and management of myelofibrosis

BCSH Guidelines 2014: Modification of British Committee for Standards in Haematology diagnostic criteria for essential thrombocythaemia

BCSH guidelines 2007: Amendment to the diagnosis, investigation and management of polycythaemia/erythrocytosis