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1. Introduction

Myeloproliferative neoplasms (MPN) conditions include essential thrombocythaemia (ET), polycythaemia vera (PV) and primary myelofibrosis (PMF). They are all closely related and have an intrinsic tendency to evolve into acute myeloid leukaemia (AML), confirming their classification as haemato-oncological disorders.

MPNs are perhaps the orphan diseases of haemato-oncology, but these patients, if managed judiciously, have prolonged survival, with a median survival greater than 10–15 years for ET and PV. However, available treatments have significant side-effect profiles and need to be chosen with care, particularly in young patients. The last decade has seen the publication of a considerable body of clinical data informing clinical decisions. Many therapeutic options, however, remain unlicensed and there have been few good quality clinical trials. The recent publication of the high frequency of mutations in calreticulin (CALR) merits their inclusion in diagnostic criteria.

The following sections contain current management protocols for ET, PV and primary MF (including MF in patients with an antecedent history of ET and PV). Management protocols for women in pregnancy and in the three months before conception are more complex and individualised; these cases should be discussed with a consultant haematologist with expertise in this area.

Other entities within the MPN group – MPNU, chronic eosinophilia, chronic neutrophilic leukaemia and mast cell disorders – are not covered in these guidelines.

These conditions listed in the World Health Organization (WHO) criteria for MPN 2008 (WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon 2008) are:

**Myeloproliferative neoplasms:**

- Chronic myelogenous leukaemia, BCR-ABL+ (CML) – see LCA Haemato-Oncology Clinical Guidelines Part 3: Chronic Myeloid Leukaemia
- Chronic neutrophilic leukaemia (CNL)
- Polycythaemia vera (PV)
- Primary myelofibrosis (PMF)
- Essential thrombocythaemia (ET)
- Chronic eosinophilic leukaemia, NOS (CEL, NOS)
- Mastocytosis
- Myeloproliferative neoplasm, unclassifiable (MPN, U)

**Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, FGFR1:**

- Myeloid and lymphoid neoplasms with PDGFRA rearrangement
- Myeloid and lymphoid neoplasms with PDGFRB rearrangement
- Myeloid and lymphoid neoplasms with FGFR1 abnormalities
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN):

- Chronic myelomonocytic leukaemia (CMML)
- Atypical chronic myeloid leukaemia, BCR-ABLneg (aCML)
- Juvenile myelomonocytic leukaemia (JMML)
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN, U)
- Provisional entity: refractory anaemia with ring sideroblasts and thrombocytosis (RARS-T)
2. Clinical Features

2.1. Essential thrombocythaemia (ET)

ET is characterised by a persistent thrombocytosis. The previously accepted platelet count threshold >600 x 10^9/L has been revised to >450 x 10^9/L. Short-term complications of ET include thrombosis and, less frequently, haemorrhage. In common with PV, long-term problems include MF and acute leukaemia, although these are less frequent in ET.

Thrombotic events affect the arterial and venous macro and microvasculature, as well as the placental circulation. Microvascular events predominate in ET typically causing erythromelalgia (asymmetric erythema, congestion and burning pain in the hands and feet), which may progress to ischaemia and gangrene, migraine-like headaches and transient ischaemic attacks (TIAs).

Approximately 30–50% of patients are symptomatic at presentation.

2.2. Polycythaemia vera (PV)

PV is characterised by an erythrocytosis (packed cell volume (PCV) >0.52 in men and >0.48 in women) and sometimes thrombocytosis and neutrophilia. The median age at presentation is 55–60 years.

Vascular thromboses, especially arterial events and more rarely bleeding, are major short-term events. In the longer term (10–15 years), MF or ‘spent phase’ occurs and AML (partially treatment related) in 5–10% of patients.

Aquagenic pruritus, gout and splenomegaly are also classical clinical features, but only occur in a few patients.

2.3. Primary myelofibrosis (PMF)

Chronic idiopathic myelofibrosis, also known as agnogenic myeloid metaplasia, PMF may arise de novo or as a late phase of ET, and particularly PV known as post-PV (PPV)-MF and post-ET (PET)-MF. Fibrosis is thought to arise from an interaction between diseased megakaryocytes, releasing mitogens such as platelet-derived growth factor (PDGF) and transforming growth factor that directly increase fibroblast proliferation.

PMF has a median age of presentation of 50–60 years. Symptoms relate to bone marrow failure (anaemia, infection, bleeding) or progressive splenomegaly (pain, weight loss, sweating). Progression to acute leukaemia occurs in up to 25% of patients (more than PV or ET) and may be associated with extramedullary collections of myeloid progenitors (chloromas).
3. Referral Pathways

Patients with a high WBC, haemoglobin/PCV or platelet count and/or suspected MPN by other means (e.g. splenomegaly, unprovoked and unusual site for a thrombotic episode) should be referred to a haematologist for assessment, via a 2 week wait pathway (see Appendix 1: 2 Week Wait Referral Forms).

All new patients should be referred to the MDT for confirmation of diagnosis, prognosis and management plan, taking into account their performance status, needs and co-morbidities (Annex 2). A joint approach with elderly care physicians and palliative care teams may be appropriate, depending on the performance status of the patient and the phase of disease.

The following patients should be referred to the MDT:

- All new patients with MPN in order to confirm the diagnosis and treatment plan
- All patients where a new line of therapy needs to be considered
- All patients with a restaging assessment
- All patients in whom an allogeneic stem cell transplant is a consideration.

Information to be captured and documented prior to, or during, the MDT includes:

- Demographic information
- Referring physician and/or GP
- Performance status
- An indicator of co-morbidities (e.g. co-morbidity score)
- Any relevant history
- Pertinent positive and negative findings on physical examination (splenomegaly, rashes, etc.)
- Spleen size (by ultrasound)
- FBC, haematinics, LFTs, U&E, LDH, urate, reticulocyte count, DAT, AIS, SPEP, serum erythropoietin, transfusion dependency
- Bone marrow aspirate and trephine histology (where available)
- Bone marrow aspirate immunophenotyping, if relevant
- Cytogenetic status (if relevant)
- Mutational status
- Specific diagnosis/category of MPN
- Other relevant imaging
- Risk score
- Availability of a clinical trial/research study and whether the patient is eligible
- Management and treatment plan
- Key worker/clinical nurse specialist
- Named consultant or team (as per local work patterns).
The MDT outcome form should be sent to the GP (by email, or preferably by fax) within 24 working hours of the MDT discussion.

Patients with PV, ET and MF may be managed at facilities with at least BSCH Level 1 designation. Complex patients may be referred to centres with specific expertise or which have available trials (see section 12: Research/Clinical Trials).

Management protocols for patients with therapy intolerance, for adults contemplating parenthood or for women during pregnancy are more complex and individualised. These patients should be discussed with a consultant haematologist who is experienced in such cases, and the patient may be referred to a subspecialist centre if needed, e.g. for obstetric care or for patients with difficult-to-manage mastocytosis.

If advice is being sought, the sub-specialist centre for such patients within the LCA is Guy’s and St Thomas’ NHS Foundation Trust:

- Professor Claire Harrison (for all clinical enquiries)
- Dr Bridget Wilkins (for trephine reviews)
- Dr Deepti Radia (for mastocytosis)

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Patients who are being considered for an allogeneic stem cell transplant should be referred to a JACIE-accredited centre (see Annex 6). Young patients with MF eligible for a transplant option should be referred for an opinion early.

3.1. Children, teenagers and young adults

Children below the age of 16 years with a diagnosis of ALL or suspected ALL must be referred to the paediatric oncology team at the principal treatment centre (PTC) and must not be managed exclusively by adult site-specific teams.

- The joint PTC for children aged below 16 years for South Thames is The Royal Marsden (Sutton)/St George’s Hospital.
- The PTC for North Thames (including North West London) is Great Ormond Street Hospital/University College London Hospitals.
- All patients <1 year from both North and South Thames should be referred to Great Ormond Street Hospital.

Please see Appendix 2 for contact information for the children’s PTCs.
3.2. Teenagers and young adults

Teenagers aged 16–18 should be managed at a PTC for teenage and young adult (TYA) cancers. Young adults aged 19–24 should be given the choice of being managed at a PTC or TYA-designated hospital.

- The PTC for TYA for South Thames is The Royal Marsden (Sutton).
- The PTC for North Thames (including North West London) is University College London Hospitals.

All patients within this age range, regardless of place of care, should be referred to the TYA MDT at the relevant PTC. Please see Appendix 3 for information about how to make a referral and contact information for the PTC and TYA-designated centres in the LCA.
4. Investigation and Diagnosis

A thorough clinical history and examination should be performed, focusing upon exclusion of secondary causes.

For patients with unprovoked blood clots (in particular of the SMA, or other unusual sites), consider checking JAK2 mutational status even if blood counts are normal.

4.1. Essential thrombocythaemia (ET)

There is no diagnostic hallmark for ET. The diagnosis is made by excluding other MPNs, and a reactive or secondary thrombocytosis. Causes of a reactive thrombocytosis include iron deficiency anaemia, chronic inflammation (e.g. rheumatoid arthritis, inflammatory bowel disease), splenectomy, acute haemorrhage, and malignant disease. In an otherwise well patient the diagnosis is generally uncomplicated. However, where conditions co-exist which may cause a reactive thrombocytosis, this may make the diagnosis more difficult.

Historically, the diagnostic criteria for ET were those of the polycythaemia vera study group. Forty years on, continual development of the diagnostic criteria for MPNs set the stage for the World Health Organization (WHO) Diagnostic Criteria 2001, modified in 2008. The revised WHO criteria require characteristic bone marrow morphology, a platelet threshold of $450 \times 10^9/L$ and molecular analysis for the JAK2 V617F mutation and other clonal markers. Modified BCSH (British Committee for Standards in Haematology) criteria or WHO criteria may be used.

**WHO (2008) diagnosis of ET: all four required**

1. Sustained plt >450 $\times 10^9/L$.
2. BM showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis.
3. Not meeting WHO criteria for PV, PM, BCR-ABL1+ CML or MDS or other myeloid neoplasm.
4. Demonstration of JAK2 V617F or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis.
Proposed BCSH diagnostic criteria for ET

**Diagnosis requires A1–A3 or A1 + A3–A5**

A1 Sustained platelet count >450 x 10^9/L

A2 Presence of an acquired pathogenetic mutation (e.g. in JAK2, CALR or MPL genes)

A3 No other myeloid malignancy, especially PV*, PMF†, CML‡ or MDS§

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 (grades 0–2/4 or grade 0/3)

* Excluded by a normal haematocrit in an iron-replete patient.
† Indicated by presence of significant bone marrow fibrosis (greater or equal to 2/3 or 3/4 reticulin) AND palpable splenomegaly, blood film abnormalities (circulating progenitors, tear-drop cells) or unexplained anaemia (Barosi et al., 1999; Mesa et al., 2007).
‡ Chronic myeloid leukaemia; excluded by absence of BCR-ABL1 fusion from bone marrow or peripheral blood.
§ Myelodysplastic syndrome; excluded by absence of dysplasia on examination of blood film and bone marrow aspirate.

Investigations to be performed on all patients include:

- FBC and blood film
- Haematinics
- Renal/liver profiles and CRP
- ANA and RhF
- Chest x-ray (most patients, all smokers)

Where there is a high index of suspicion on first appointment, otherwise at second visit:

- JAK2 V617F, CALR and MPLW515L/K screen
- Abdominal ultrasound scan
- Bone marrow aspirate and trephine (BMAT), cytogenetics in all patients <60 years, JAK2/MPL/CALR mutation negative patients and patients where there is a suspicion of MDS or MF, regardless of mutation status
- Samples sent for bcr-abl FISH to exclude a diagnosis of CML
- Consider testing for vWFAg and Ricof looking for acquired VWD in patients with platelets >1000 x 10^9/L and haemorrhagic symptoms

BMAT should be performed in all patients under 60 years, and JAK2/CALR/MPL mutation negative patients and patients where there is a suspicion of MDS regardless of mutation status. Bone marrow aspirate (BMA) samples should also be sent for cytogenetics and FISH for bcr-abl to exclude a diagnosis of CML. In patients not requiring a BMAT, i.e. typical findings in a JAK2 V617F positive and patient is over 60 years, a peripheral blood sample should be sent for bcr-abl. The decision to proceed to formal cytogenetic analysis on any sample received is made at the diagnostic multidisciplinary (MDT) meeting.
The recent WHO criteria for ET place greater emphasis upon bone marrow histology, in particular megakaryocyte morphology, but this has not gained wide acceptance. The other condition that must be excluded when diagnosing ET is myelodysplastic syndrome. This is usually associated with a low rather than high platelet count and is characterised by dysplastic features morphologically and particular chromosomal abnormalities. Note that some patients with refractory anaemia with ring sideroblasts (RARS) or chromosome 5 abnormalities and MDS may also carry the JAK2 V617F mutation (see WHO classification for MDS-RARS-T).

4.2. Polycythaemia vera (PV)

An erythrocytosis is defined as a PCV >0.52 in men and >0.48 in women. To determine whether there is an absolute erythrocytosis (increased red cell mass [RCM]) or an apparent/pseudo-erythrocytosis (normal RCM, reduced plasma volume), an RCM study is performed. This has been largely superseded by testing for the presence of the JAK2 V617F mutation which indicates the presence of an MPN or an MDS. The JAK2 V617F mutation negative erythrocytosis cases may still be a PV case without a genetic marker or with a JAK2 exon12 mutation; alternatives include a pseudo/apparent, primary congenital, secondary congenital or acquired, or idiopathic erythrocytosis, all of which require definition.

The current BCSH erythrocytosis guideline amendment suggests a three-stage approach to investigation. The procedure outlined below is an adaptation of this guidance, based upon modified diagnostic criteria suggested by Campbell and Green (2006), simplifying the diagnosis and the need for investigation in JAK2-positive PV. Determination of a case of JAK2 negative PV or an alternative cause of erythrocytosis will require further investigation.

<table>
<thead>
<tr>
<th>JAK2 positive PV (Diagnosis requires both to be present)</th>
</tr>
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<tbody>
<tr>
<td>A1  PCV &gt;0.52 men, &gt;0.48 in women or a raised RCM (&gt;25% above predicted)</td>
</tr>
<tr>
<td>A2  Mutation in JAK2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>JAK2 negative PV (Diagnosis requires A1 + A2 + A3 + either another A or two B criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1  Raised RCM (&gt;25% above predicted) or a PCV &gt;0.60 in men, &gt;0.56 in women</td>
</tr>
<tr>
<td>A2  Absence of mutation in JAK2</td>
</tr>
<tr>
<td>A3  No cause of secondary erythrocytosis</td>
</tr>
<tr>
<td>A4  Palpable splenomegaly</td>
</tr>
<tr>
<td>A5  Presence of acquired genetic mutation (excluding BCR-ABL) in haemopoietic cells</td>
</tr>
<tr>
<td>B1  Thrombocytosis: platelet count &gt;450 x 10^9/L</td>
</tr>
<tr>
<td>B2  Neutrophil leukocytosis</td>
</tr>
<tr>
<td>B3  Radiological evidence of splenomegaly</td>
</tr>
<tr>
<td>B4  Endogenous erythroid colonies or low serum erythropoietin</td>
</tr>
</tbody>
</table>

The primary clinical assessment of an erythrocytosis case should include a thorough history and examination seeking out possible secondary causes, followed by Stage 1 investigations to confirm or refute a diagnosis of a JAK2 V617F positive PV. The majority of patients (excluding borderline erythrocytosis) and all ex- and current smokers will require a chest x-ray. Urinalysis is a simple effective screen for renal disease, which should be performed in all patients at the initial visit. Patients may present with
co-morbidity; thus, regardless of a diagnosis of PV, a review of secondary causes is pertinent. Additional investigation of possible secondary causes will vary according to symptoms or signs present.

**PV Stage 1:**
- FBC and blood film
- Haematinics
- Renal, liver profile and urate level
- JAK2 V617F
- Chest x-ray (smokers)
- Urinalysis
- Serum erythropoietin level
- Pulse oximetry and venous carboxyhaemoglobin

If the initial screening tests are negative for a JAK2 mutation and there is no obvious secondary cause, further investigations are indicated. An RCM may be required to define whether a case is a pseudo/apparent or an absolute erythrocytosis at this point and should be discussed with the consultant. A PCV of >0.60 and >0.56 in a man or woman, respectively, can be assumed to have an absolute erythrocytosis and an RCM would not be indicated. Cases confirmed as an absolute erythrocytosis require Stage 2 tests, as appropriate, with consultant guidance.

**PV Stage 2:**
- Strongly consider BMAT for JAK2 V617F positive patients <60 (required if there is evidence or suspicion of MDS or MF) and JAK2 V617F negative patients with a strong suspicion of PV (clinician choice if age >60)
- Cytogenetics
- Peripheral blood for JAK2 exon12 screen in a JAK2 V617F negative patient with a strong suspicion of PV
- Abdominal ultrasound
- Erythroid burst-forming unit culture (BFU-E): if test available and considered appropriate, discuss with consultant
- RCM performed in nuclear medicine – discuss with consultant

The serum erythropoietin level, JAK2 exon12 mutation screen, abdominal ultrasound and, in very specific cases, BFU-E culture will aid the diagnosis of JAK2 V617F negative PV. Hypoxaemia causing a secondary erythrocytosis can be screened for by assessing oxygen saturation using pulse oximetry (92% is the arbitrary cut-off for significance) and the carboxyhaemoglobin level available from biochemistry. It is important to subtract the carboxyhaemoglobin level from the oxygen saturation to obtain the correct estimate of oxygen saturation. The abdominal ultrasound combined with urinalysis and GFR estimation enables a renal disease screen.
A BMAT should be performed in all cases of JAK2 V617F negative absolute erythrocytosis where no cause of secondary erythrocytosis is found. Although the Green and Campbell criteria do not include histology as a diagnostic criterion, the presence of typical histology will support a diagnosis of JAK2 negative PV, whereas its absence will suggest an alternative cause. Recently, WHO has proposed new criteria, included below for comparison, which place significant emphasis on bone marrow histology and have yet to gain widespread credence. A baseline BMAT should also be obtained in all JAK2 V617F positive patients who are under 60 for future reference regarding progression, although it is not essential to confirm a diagnosis. A BMA sample should be sent for cytogenetics – the decision whether to formally proceed to assess these samples is made in the diagnostic MDT meeting.

**Table 1: WHO diagnosis of PV**

Need both major and one minor criteria OR major criterion no.1 with two minor criteria (after exclusion of secondary causes)

<table>
<thead>
<tr>
<th>Major</th>
<th>Hb&gt;18.5g/dL or PCV &gt;0.51 (male); Hb&gt;16.5g/dL or PCV &gt;0.48 (female) or other evidence of increased red cell volume. Presence of JAK2 V617F or other functionally similar mutation (e.g. JAK2 exon12).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>BM hypercellular for age with trilineage growth (panmyelosis) and prominent erythroid/granulocytic/megakaryocytic proliferation. Serum EPO level below normal. Endogenous erythroid CFU <em>in vitro</em>.</td>
</tr>
</tbody>
</table>
4.3. Primary myelofibrosis (PMF)

For diagnosis of PMF, exclude other MPNs (PV, ET and CML) and disorders in which marrow fibrosis can develop as a secondary feature (e.g. metastatic carcinoma, lymphoma, irradiation, TB and leishmaniasis).

The following are generally necessary to confirm PMF:

- Splenomegaly
- Increased BM fibrosis. In later stages, new osteoid is formed (osteomyelofibrosis)
- Leucoerythroblastic blood film
- Absence of other MPN, including CML (perform FISH for bcr-abl)
- Exclude secondary causes of myelofibrosis (see above)
- It may be useful to obtain an LDH level and cytogenetics periodically to monitor.

The following tests should be performed:

- FBC and blood film, blast count
- Haematinics
- Renal, liver profile, LDH and urate level
- JAK2 V617F, CALR and MPL W515L/K screen
- Chest x-ray
- Abdominal ultrasound scan
- BMAT with samples sent for cytogenetics and FISH for bcr-abl.

**Table 2: WHO diagnosis of PMF: need to meet all three major and two minor criteria**

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
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</table>
| Megakaryocyte proliferation and atypia, usually with either reticulin and/or collagen fibrosis, or by increased BM cellularity characterised by granulocytic proliferation and often decreased erythropoiesis (i.e. prefibrotic cellular-phase disease). Not meeting WHO criteria for PV, BCR-ABL1+ CML, MDS or other myeloid neoplasms. JAK2 V617F+ or other clonal marker (e.g. mpl) or no evidence that BM fibrosis /changes are secondary to infection, AI disorder or other chronic inflammatory condition, HCL or other LPD, metastatic cancer, or toxic (chronic) myelopathies. | Leukoerythroblastosis  
Increase in serum LDH  
Anaemia  
Splenomegaly |
**BCSH diagnostic criteria for PMF: requires A1 + A2 and any two B criteria**

A1  Bone marrow fibrosis $\geq$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  Palpable splenomegaly
B2  Unexplained anaemia
B3  Leucoerythroblastic blood film
B4  Tear-drop red cells
B5  Constitutional symptoms¹
B6  Histological evidence of extramedullary haematopoiesis

**BCSH diagnostic criteria for post-PV and post-ET MF: requires A1 + A2 and any two B criteria.**

A1  Bone marrow fibrosis $\geq$3 (on 0–4 scale)
A2  Previous diagnosis of ET or PV
B1  New palpable splenomegaly or increase in spleen size of $\geq$5cm
B2  Unexplained anaemia with 2g/dL decrease from baseline haemoglobin
B3  Leucoerythroblastic blood film
B4  Tear-drop red cells
B5  Constitutional symptoms*¹
B6  Histological evidence of extramedullary haematopoiesis

*¹ Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37.5°C) or diffuse bone pains.

### 4.4. Pathology

**Careful attention must be paid to the labelling of forms and samples before sending to the Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS). Samples are unlikely to be processed unless clearly and correctly labelled.**

**BMAT (See Annex 1):**

- Slides for morphology to SIHMDS lab
- 2–5ml in EDTA for immunophenotyping with a slide
- 2–5ml in EDTA for molecular genetics
- 2–5ml in heparin (PFH or lithium heparin) for cytogenetics/FISH
- Trephine for histopathology

For contact details for SIHMDS or current diagnostic services please see Annex 5.

### 4.5. Imaging

All patients should have an ultrasound of the abdomen performed at diagnosis to document spleen (and liver) size, and thereafter when clinically appropriate.
5. Risk Stratification

5.1. Essential thrombocythaemia (ET)

**Conventional and BCSH risk stratification**

High risk ET ANY ONE of the following factors:

- Age >60 years
- Platelet count >1500 $\times 10^9$/L
- Previous thrombosis, erythromelalgia (if refractory to aspirin)
- Previous haemorrhage related to ET
- Diabetes or hypertension requiring pharmacological therapy*
- Pregnant patients with pregnancy-related complications in previous or current pregnancy – these patients revert to original risk group 6/52 post-partum

Low risk ET** patients <40 years lacking any of the above markers of high-risk disease

Intermediate risk ET** patients 40–60 years lacking any of the above markers of high-risk disease

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5.2. Polycythaemia vera (PV)

**Conventional risk stratification**

High risk PV ANY ONE of the following:

- Age >60 years
- Previous documented thrombosis, erythromelalgia (if refractory to aspirin)
- Platelets >1000 $\times 10^9$/L*
- Diabetes or hypertension requiring pharmacological therapy*
- Significant (i.e. >5cm below costal margin on palpation) or symptomatic (pain, early satiety) splenomegaly. NB this may be an indication for treatment rather than a risk factor *per se* *

Low risk PV: patients not having any of the above risk factors.

---

* Predicts thrombosis.
* These risk factors are more controversial and have not been fully agreed, e.g. what degree of leukocytosis or grade of reticulin.
** These categories are contentious and some recommend low and high risk only, or classify individuals with cardiovascular risk factors as intermediate risk.

---

* Predicts thrombosis but not tested prospectively.
* These risk factors are more controversial and have not been fully agreed.
BCSH PV risk stratification:

**High-risk patients**

Any one of the following:

- Age >60 years and/or a platelet count >400–600 x 10⁹/L (highly variable threshold)
- History of thrombotic or haemorrhagic complications, diabetes, vascular disease or hypertension
- Pregnant patients with pregnancy-related complications in current or previous pregnancy for the duration of pregnancy

**Intermediate-risk patients**

- Age 40–60 years
- No thrombotic or haemorrhagic complications, diabetes, vascular disease or hypertension
- Platelet count <400–600 x 10⁹/L (highly variable threshold)

**Low-risk patients**

- Age <40 years
- No thrombotic or haemorrhagic complications, diabetes, vascular disease or hypertension
- Platelet count <400–600 x 10⁹/L (highly variable threshold)

5.3. Primary myelofibrosis (PMF)

The most widely adopted risk stratification was validated on 1,500 PMF patients: the International Prognostic Scoring System IPSS (Cervantes 2008). But this applies to patients at diagnosis only. Subsequent studies have shown that the high-risk features of the IPSS can be applied in a dynamic manner to give useful prognostic information during follow-up of MF patients (DIPSS, Passamonti 2010). The most recent scoring system is the DIPSS-Plus (Gangat 2011), which takes into account transfusion dependence and thrombocytopenia.

None of these have been validated for post-ET or post-PV MF.

**Table 3: IPSS, DIPSS and DIPSS-plus scoring for MF with prognostic chart**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPSS</th>
<th>DIPSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Haemoglobin &lt;10g/dL</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count &gt;25x10⁹/L</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Circulating blasts &gt;1%</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

1 point each but Hb=2
### DIPSS-plus add one to the DIPSS score for each of:

- Platelet count <100 x 10⁹/L
- RBC transfusion need
- Unfavourable karyotype
  +8,-7/7q-;i(17q);inv(3), -5/5q-;12p-, 11q23 rearr.

### Linking scores to prognosis:

<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>Int-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>Int-2</td>
<td>2</td>
<td>4</td>
<td>3 or 4</td>
<td>4</td>
<td>2–3</td>
<td>2.9</td>
</tr>
<tr>
<td>High</td>
<td>&gt;3</td>
<td>2.3</td>
<td>5 or 6</td>
<td>1.5</td>
<td>&gt;4</td>
<td>1.3</td>
</tr>
</tbody>
</table>
6. Patient Information/Support

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist. The LCA has produced a key worker policy (see Appendix 4: LCA Key Worker Policy) which sets out the definition of a key worker and provides an overview of their role and responsibilities.

The clinical nurse specialist/key worker should be present at diagnosis and at any significant discussion where treatment changes and outcomes are discussed. In the absence of the clinical nurse specialist, a senior nurse may deputise who must ensure that all conversations are documented in the patient’s notes and on the electronic patient record. Where it is not possible for the clinical nurse specialist or a deputy to be present, patients should be given the clinical nurse specialist’s contact numbers. The clinician leading the consultation should advise the clinical nurse specialist who should then arrange to make contact with the patient.

The clinical nurse specialist should ensure that all patients are offered a holistic needs assessment (HNA) (see Appendix 5: LCA Holistic Needs Assessment Tool) at key pathway points, including within 31 days of diagnosis; at the end of each treatment regime; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

Information booklets are available to download from the Leukaemia & Lymphoma Research, Macmillan Cancer Support, MPN voice and NHS information prescription service websites:

https://leukaemialymphomaresearch.org.uk/information/other-blood-cancers/myeloproliferative-neoplasms-mpn

www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx

www.mpnvoice.org.uk

www.nhs.uk/ipg/pages/ipstart.aspx

Patients should have access to supportive care information and rehabilitation throughout the cancer pathway. Consider referral to the appropriate services, including rehabilitation, when indicated. Please refer to section 11: Rehabilitation and Survivorship.
7. Treatment

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide/HU), anagrelide, interferon-alpha, ruxolitinib, busulfan or radioactive phosphorus.

When discussing oral treatments with patients for the first time, ensure that the Oral Chemotherapy Patient Education Checklist (Annex 3) is used and signed off. Patient hand-held dosing booklets (for HU and ANA) may be available in some centres.

7.1. Essential thrombocythaemia (ET)

7.1.1. Management and prognosis

Patients with ET, akin to those with PV, are predisposed to thrombosis, which is a major cause of morbidity and mortality. Haemorrhage occurs less frequently and is particularly associated with platelet counts in excess of 1500 x 10⁹/L and acquired von Willebrand disease.

Initial management should address lifestyle issues and risk factors associated with vascular events, including smoking, diabetes, hypertension and hyperlipidaemia. Most patients would benefit from 75mg aspirin daily or alternative anti-platelet drugs. The exceptions are those with active haemorrhage, aspirin intolerance, active or previous peptic ulcer disease, and, in those patients with platelets >1000 x 10⁹/L, acquired von Willebrand disease should be excluded first by testing vWF:Ag and ristocetin cofactor activity.

The likelihood of thrombosis and haemorrhage is significantly reduced by therapy to control the platelet count to <400 x 10⁹/L. The current gold standard cytoreductive drug is hydroxyurea/hydroxycarbamide (HU). Alternatives include ³²P and busulfan, although these agents are more leukaemogenic. Interferon (IFN)-α controls the platelet count in a majority of patients, but is poorly tolerated with up to 30% being unable to continue treatment in the long term. IFN and anagrelide (ANA) have the advantage of being non-leukaemogenic and they preserve fertility. The MRC-PT1 study made a direct comparison between HU and ANA in patients with ET. The results of the high-risk arm suggest that HU + aspirin is a more effective first-line therapy than ANA + aspirin, which was associated with a higher rate of arterial thrombosis, haemorrhage and myelofibrotic transformation. A randomised trial to compare HU versus IFN would be of benefit to further evidence-based practice.

As survival in ET is long and cytoreductive agents have a poor side-effect profile, current practice would be to use these agents only in patients with a high risk of thrombosis. This would include patients aged over 60 or with any of the following risk factors: a prior thrombosis, diabetes, hypertension, vascular disease or a platelet count >1500 x 10⁹/L. For patients under 40 with none of these risk factors, aspirin alone is probably sufficient. For patients aged between 40 and 60 and lacking any of the risk factors, the management strategy is far from clear. Best practice would be to randomise such patients into an appropriate clinical trial, if available.

7.1.2. Aims of treatment

The aims of treatment are to reduce the incidence of thrombotic and haemorrhagic complications and potentially reduce long-term risk of transformation to myelofibrosis.
7.1.3. Evidence

- HU reduces the incidence of thrombotic episodes in high-risk patients according to a randomised controlled trial (Cortelazzo et al. 1995).
- ANA may be inferior to HU according to the results of the high-risk arm of the MRC-PT1 study (Harrison 2005).
- There is no evidence on which to base a management strategy for intermediate- or low-risk patients (Harrison 2002).
- There is evidence that HU reduces long-term risk of transformation to myelofibrosis in PV, although there is no direct evidence for ET (Najean et al. 1996).

7.1.4. Treatment protocol

- Identify and aggressively manage all reversible risk factors for arterial disease including smoking, hypercholesterolaemia, hypertension and diabetes.
- Aspirin for all in absence of contraindications as above. Consider screen for acquired von Willebrand disease in those with platelets >1000 x 10⁹/L.

Evidence grade level overall Ib -III

High-risk patients

First-line therapy is HU.

Ensure counselling of all patients of reproductive age regarding teratogenicity. Uncertain effects upon fertility in long-term use and reiterate necessity for contraception (see above).

Evidence grade level Ib

Second-line therapy (in those patients refractory/intolerant to first-line therapy or developing PMF or progressive splenomegaly):

- Patients aged >70 years, consider busulfan or combination therapy with ANA and HU.
- Patients aged <70 years, consider either IFN or ANA or combination therapy with ANA and HU or consider pegylated interferon alpha 2A (see restrictions above).

Evidence grade level III

Intermediate- and low-risk patients

The MRC-PT1 trial (closed to recruitment) is currently evaluating treatment for these patient groups and best therapy is currently unclear. Intermediate-risk patients may receive either aspirin alone or aspirin and hydroxyurea. Low-risk patients may receive aspirin. Discuss with consultant. Consider recruiting into an appropriate clinical trial or research study.
Treatment Summary Box: Essential thrombocythaemia

- **ALL** patients – assess and manage cardiovascular risk factor; screen for disease-related symptoms
- **TREAT WITH** low dose aspirin (unless contraindicated)
- **HIGH-RISK PATIENTS***
  
  >60* years
  1st line: Hydroxycarbamide
  2nd line: consider clinical trial or interferon**, anagrelide*** alone or in combination; if
  >75 years busulfan or 32P
  <60* years
  1st line: hydroxycarbamide or interferon**
  2nd line: consider clinical trial; interferon**, anagrelide*** alone or in combination

* Treatment recommendations made for high-risk patients only, high-quality clear evidence for low or intermediate risk ET or PV management is unclear.
** Not currently licensed for this indication.
*** Current British guidelines recommend regular monitoring of patients treated with anagrelide for the development of fibrosis28, 42

7.1.5. Treatment options

Aggressively manage all reversible risk factors for arterial disease.

Patient leaflets are available for all treatment options from the Macmillan website.

Pre-chemotherapy counselling is available from the CNS/key worker (Appendix 4). Counselling session should be followed up one week later with a telephone consultation.

**Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxycarbamide (hydroxyurea), anagrelide, interferon alpha, busulfan or radioactive phosphorus.**

**Aspirin**

75mg per day for all patients without a clear contraindication (asthma, history of peptic ulceration, haemorrhage, platelet count in excess of 1000 x 109/L).

**Hydroxyurea/hydroxycarbamide**

Refer to local or regional protocol. HU is the only treatment with demonstrated benefit in a randomised controlled trial; benefit for intermediate-risk patients is currently being assessed in the MRC-PT1 study. Limiting side effects include leukaemogenicity (3–5% with single agent usage, increasing to 15–30% in combination with alternative leukaemogenic agents (Murphy et al. 1997, Sterkers et al. 1998)), teratogenicity and the development of a refractory state in 10–15% of patients.
Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HU and discuss alternative treatment if necessary with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if necessary with IFN.

Interferon
Refer to local or regional protocol. IFN reduces the risk of complications in high-risk patients; unfortunately up to 30% of patients are not able to tolerate IFN due to the side effects. It is a suitable second-line agent and also the only treatment currently used in pregnancy (Harrison 2002). Pegylated-IFN may have some benefit in patients not tolerating conventional IFN.

Pegylated interferon (PEGASYS)
This agent has a similar utility to conventional interferon. It is currently approved for the treatment of patients who are refractory or intolerant to first-line therapy. There are some early data suggesting it is useful in this setting (Rea et al. 2009). Intolerance to therapy would include development of side effects that would lead to therapy introduction, and refractory disease is defined as inability to reach therapeutic targets without causing dose-limiting toxicity or unacceptable cytopenia. There are also provisional data suggesting it may induce molecular remissions in some patients with ET or PV (Kiladjian et al. 2008), and also significant responses in patients with PMF (Ianotto et al. 2009). This agent should ONLY be prescribed by a consultant and ONLY when funding has been approved. Refer to local or regional protocol.

For all interferons it is important to screen twice yearly for liver and thyroid disease, as well as surveillance for depression.

Anagrelide
Refer to local or regional protocol. ANA is currently licensed for high-risk patients as a second-line agent for patients refractory or intolerant of first-line therapy. Limitations include cardiac toxicity and teratogenicity. Preliminary data from the MRC-PT1 study suggest ANA is not as effective as HU in preventing thrombotic and haemorrhagic complications, and is associated with greater risk of progression to myelofibrosis. The risk of bleeding should be assessed and considered prior to the concomitant use of aspirin.

ANA may be usefully given in combination with HU in some patients.

Prior to commencing ANA, all patients must have a chest x-ray and ECG. An echocardiogram should be performed in those with a previous cardiac history or abnormal ECG, or increased cardiothoracic ratio on chest x-ray. Further evaluation is required if patients become symptomatic. Consider referral to a cardiologist if indicated.

Busulfan
Refer to local or regional protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Use is limited to second line in patients over 65 years of age due to the associated risk of leukaemia. Discuss with consultant haematologist.
**32Phosphorus**

Phosphorus is a historical treatment which has an even higher incidence of leukaemic transformation than treatment with busulfan. Hence it is reserved for the very elderly or patients in whom one cannot ensure compliance with medications. A medical consent generated by nuclear medicine should be completed by the haematology department. **Discuss with consultant haematologist.**

**JAK inhibitors/HDACs**

For refractory or intolerant patients, consider entry into a clinical trial for use of a novel agent.

### 7.2. Polycythaemia vera (PV)

#### 7.2.1. Management and prognosis

Thrombosis is the major cause of death in untreated patients whose median survival is only 18 months. Control of the elevated PCV is achieved by repeated venesection or cytoreductive therapy (especially if the platelet count is elevated). The target PCV is <0.45 (this may be reduced in patients remaining symptomatic), and platelets <400 x 10^9/L. Antiplatelet drugs, traditionally aspirin and alternatives including clopidogrel in patients resistant or intolerant of aspirin, have a role. In earlier PVSG studies larger doses of aspirin (900mg) were associated with increased haemorrhage. The ECLAP study demonstrated the benefit of aspirin in reducing thrombotic events (Landolfi *et al.* 2004). Aspirin is contraindicated in those with known aspirin intolerance, active or previous peptic ulcer disease, or prominent bleeding symptoms.

Where the platelet count is >1000 x 10^9/L, the presence of acquired von Willebrand disease should first be excluded by measurement of RiCOF and vWF:Ag.

HU is the standard cytoreductive drug used to treat PV and other MPNs. It is generally well tolerated but there is some anxiety that it might increase the risk of leukaemia. Historically 32Phosphorus and busulfan were used, but their use is restricted because of their well-defined leukaemogenic potential. Emerging therapies include IFNα, pegylated-IFN and ANA, with the dual advantages of preserving fertility and being non-leukaemogenic.

Treated patients have a median survival of at least 8–15 years and are then at risk of transformation to myelofibrosis or ‘spent phase’. This phase of the disease is characterised by progressive splenomegaly and pancytopenia, and is generally treated supportively; for a minority of patients bone marrow transplantation is an option. AML is a terminal feature of PV and is usually refractory to treatment. However, options include an AML protocol or cytarabine (unlicensed and unfunded indication) or, for example, azacitidine (unlicensed and unfunded indication). Most patients, however, respond very poorly. A clinical trial with novel agents should be sought in the case of AML transformation.

#### 7.2.2. Aims of treatment

The aim is to reduce the incidence of thrombotic and haemorrhagic complications and the long-term risk of transformation to myelofibrosis.
7.2.3. Evidence

- Control of haematocrit and thrombocytosis reduces thrombotic complications according to the PVSG trials (Berk 1986 and Najean 1994).
- Cytoreductive therapy compared to venesection alone reduces the incidence of myelofibrosis (Najean 1996).
- Patients with a high platelet count are at particular risk of MF (Najean 1996).
- Target HCT is 0.45 (Barbui et al. 2013).

7.2.4. Treatment protocol

- Aggressively manage all reversible risk factors for cardiovascular disease.
- Aspirin should be considered in all cases in absence of contra-indications as above.

**Evidence grade level I**

**High-risk patients**

First-line therapy is HU.

Ensure counselling of all patients of reproductive age regarding teratogenicity potential and long-term effects upon fertility, and reiterate necessity for contraception.

**Evidence grade level III**

Second-line therapy (in those patients refractory/intolerant to first-line therapy or developing PMF or progressive splenomegaly on hydroxycarbamide):

- Patients aged >70 years – busulfan or consider combination therapy with HU and ANA or PEG-interferon, but see restrictions above.
- Patients aged <70 years – consider IFN or consider combination therapy with HU and ANA.
- Or treatment as for myelofibrosis.

**Evidence grade level IV**

**Intermediate- and low-risk patients**

First-line treatment is venesection alone. Monitor if repeat BM suggests development of myelofibrosis or if spleen enlarges add cytoreductive therapy as for high-risk patients above.

**Evidence grade level IV**
Treatment Summary Box: Polycythaemia vera

- **ALL** patients – assess for and manage cardiovascular risk factors; screen for disease-related symptoms
- **TREAT** with low dose aspirin (unless contraindicated); venesect to target PCV 0.45
- **HIGH-RISK PATIENTS***

>60* years
1st line: hydroxycarbamide or interferon
2nd line: consider clinical trial or interferon**, if >75 years busulfan or $^{32}$P

<60* years
1st line: interferon**
2nd line: consider clinical trial or hydroxycarbamide, or anagrelide**. ***

* Treatment recommendations made for high-risk patients only, high-quality clear evidence for low or intermediate risk ET or PV management is unclear.
** Not currently licensed for this indication.
*** Current British guidelines recommend regular monitoring of patients treated with anagrelide for the development of fibrosis.28, 42

7.2.5. **Treatment options**

Aggressively manage all reversible risk factors for arterial disease.

Patient leaflets are available for all treatment options from the Macmillan Cancer Support website.

Pre-chemotherapy counselling is available from the CNS/key worker (Appendix 4). Counselling session should be followed up one week later with a telephone consultation.

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide), anagrelide, interferon alpha, busulfan or radioactive phosphorus.

**Venesection**

To maintain PCV less than 0.45. Coulter counters underestimate PCV when patients have microcytic, hypochromic indices – a correction factor is available (discuss with a consultant). In patients with a platelet count $>400 \times 10^9/L$, there is a possible increased risk of complications and myelofibrosis if treated by venesection alone.

**Aspirin**

A dose of 75mg per day should be considered for all patients without clear contraindication (asthma, history of peptic ulceration, haemorrhage, platelet count in excess of $1000 \times 10^9/L$).

**Hydroxyurea/hydroxycarbamide (HU)**

Refer to local chemotherapy protocol. The benefit of HU is demonstrated in the PVSG study (Berk 1986, GISP). Limiting side effects include leukaemogenicity (3–5% with single agent usage, increasing to 15–30%)
in combination with alternative leukaemogenic agents (Murphy et al. 1997, Sterkers et al. 1998), teratogenicity and the development of a refractory state in 10–15% of patients.

**Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HU and discuss alternative treatment if appropriate with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if appropriate with IFN.**

**Interferon**

Refer to the local chemotherapy protocol. There is evidence of a reduction in the risk of complications (Reilly 1996, Radin 2003). Unfortunately up to 30% of patients are not able to tolerate IFN due to the side effects. IFN is a suitable second-line agent and the sole agent currently used in pregnancy. Pegylated-IFN may have some benefit in patients not tolerating conventional IFN.

**Pegylated-interferon**

This agent has a similar utility to conventional interferon. It is currently approved for treatment of patients who are refractory or intolerant to first-line therapy, and there are some early data suggesting it is useful in this setting (Rea et al. 2009). Intolerance to therapy would include development of side effects that would lead to therapy introduction, and refractory disease is defined as inability to reach therapeutic targets without causing dose-limiting toxicity or unacceptable cytopenia. There are also provisional data suggesting it may induce molecular remissions in some patients with ET or PV (Kiladjian et al. 2008) and also significant responses in patients with PMF (Ianotto et al. 2009). This agent should ONLY be prescribed by a consultant haematologist and ONLY when funding has been approved. Refer to the local chemotherapy protocol.

For all interferons, it is important to screen twice yearly for liver and thyroid disease, as well as surveillance for depression.

**Anagrelide**

Refer to the local chemotherapy protocol. There is evidence of a reduction of complications in high-risk ET patients in observational but not in comparative studies. The numbers of patients with PV in these studies is small (Anagrelide Study Group 1992). See further comments under section 7.1: Essential thrombocythaemia. The risk of bleeding should be assessed and considered prior to the concomitant use of aspirin.

ANA may be used in combination with HU in selected patients.

**Busulfan**

Refer to the local chemotherapy protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide is. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Its use is limited to patients over 65 due to the
associated risk of leukaemia, in whom it is a second-line therapy in those patients refractory/intolerant to HU. Discuss with consultant haematologist.

**32Phosphorus**

Phosphorus is a historical treatment which has an even higher incidence of leukaemic transformation than treatment with busulfan. Hence it is reserved for the very elderly or patients in whom one cannot ensure compliance with medications. Orders are via EPR; a medical consent generated by nuclear medicine should be completed by the haematology department. Discuss with consultant haematologist.

**7.3. Primary (or secondary) myelofibrosis (PMF, PPV-MF, PET-MF)**

**7.3.1. Management and prognosis**

Supportive therapy with red cell transfusions and treatment of infection is a mainstay with androgens or erythropoietin therapy for some. Chemotherapy, in particular with hydroxyurea/hydroxycarbamide, may be useful initially to reduce splenomegaly and slow/reduce fibrosis, although this may not affect prognosis. Thalidomide is of interest but is toxic and not beneficial for most; it may be best used as a low dose with steroids. Studies with the tyrosine kinase inhibitor (imatinib), a designer drug for treatment of CML, appear to be disappointing. The response of patients to JAK2 inhibitors will be of interest over the next few years.

In advanced disease, splenectomy is an option but has significant morbidity rates and is not generally recommended; splenic irradiation may be useful. Allogeneic stem cell transplantation may cure a small number of patients but, due to high procedure-related mortality, it has only been performed in young patients with poor prognosis. Recently, low intensity allogeneic transplants with reduced procedure-related mortality have been useful. Autologous stem cell transplants have proven unsuccessful in patients with stem cells harvested in advanced phase. The role of autologous stem cells harvested early in the disease remains unclear and has fallen from favour.

Use an IPSS, DIPSS or DIPSS-plus score for prognosis in PMF – these have not been validated in PET- or PPV-MF (see section 5: Risk Stratification).

**7.3.2. Aims of treatment**

- Control symptoms of disease (transfusions)
- Reduce incidence of thrombotic and haemorrhagic complications
- Reduce disease progression.

**7.3.3. Treatment protocol**

**Intermediate- and high-risk patients**

Tissue type and refer for stem cell transplant discussion if less than 65–70 years and sufficiently fit. Consider agents below as per specific indications.

**Low-risk patients**

Tissue type siblings if under 60 to inform future therapy.

If progress, treat as for high-risk patient.

If thrombocytosis or develop thrombotic or haemorrhagic complications treat with hydroxyurea.
Evidence grade level IV

7.3.4. Treatment options

Also see comments under section 7.1: Essential thrombocythaemia.

Aggressively manage all reversible risk factors for arterial disease.

Patient leaflets are available for all treatment options from the Macmillan website.

Pre-chemotherapy counselling is available from the CNS/key worker (Appendix 4).

Counselling session should be followed up one week later with a telephone consultation.

Formal written consent should be obtained for all patients before commencing any cytoreductive therapy (red cell-, white cell- or platelet-controlling drugs) including hydroxyurea (hydroxycarbamide), anagrelide, interferon alpha, busulfan or radioactive phosphorus.

Aspirin

75mg per day should be considered in all patients without clear contraindication (asthma, history of peptic ulceration, haemorrhage, laboratory evidence of acquired von Willebrand disease, or a platelet count in excess of 1000 or a platelet count <50 x 10^9/L).

Ruxolitinib

The JAK2 inhibitor ruxolitinib is currently available for first- or second-line use in MF patients via the Cancer Drugs Fund (CDF). Evidence from the COMFORT and COMFORT-2 studies indicates that ruxolitinib is effective in reducing spleen size and associated symptoms, and improves overall quality of life. Refer to the local chemotherapy protocol. Patients must meet the CDF criteria and a funding application must be made prior to commencement of treatment. Refer to the NHS England website for further information about funding: www.england.nhs.uk/ourwork/pe/cdf/

Hydroxyurea/hydroxycarbamide (HU)

Refer to the local chemotherapy protocol. Limiting side effects include leukaemogenicity (3–5% with single agent usage, increasing to 15–30% in combination with alternative leukaemogenic agents (Murphy et al. 1997, Sterkers et al. 1998)), teratogenicity and the development of a refractory state in 10–15% of patients.

Prior to conception, a three-month wash-out period is required. Women should be reviewed, stop HU and discuss alternative treatment if appropriate with IFN. Similarly, men wishing to father a child should discontinue HU three months prior to planned conception and discuss treatment if appropriate with IFN.

Thalidomide

Recent evidence suggests that low doses of thalidomide (50mg) in combination with a reducing dose of prednisolone commencing 1mg/kg may be beneficial and less toxic than doses used previously (Mesa 2003, Giovanni 2002). Some patients develop worsening thrombocytosis and extramedullary haemopoiesis. In patients with a previous history of thrombosis, low molecular weight heparin prophylaxis should be considered. All thalidomide is prescribed via the Pharmion risk management system by a registered prescriber. This is an unlicensed indication for thalidomide and is not funded by NHS England.
Interferon
Refer to the local chemotherapy protocol. There is limited evidence of benefit in reducing disease progression; unfortunately up to 30% of patients are not able to tolerate IFN due to the side effects. IFN is a suitable second-line agent and the only treatment currently used in pregnancy.

Pegylated-interferon
This agent has a similar utility to conventional interferon. It is currently approved for treatment of patients who are refractory or intolerant to first-line therapy. There are some early data suggesting it is useful in this setting (Rea et al. 2009). Intolerance to therapy would include development of side effects that would lead to therapy introduction, and refractory disease is defined as inability to reach therapeutic targets without causing dose-limiting toxicity or unacceptable cytopenia. There are also provisional data suggesting it may induce molecular remissions in some patients with ET or PV (Kiladjian et al. 2008) and also significant responses in patients with PMF (Ianotto et al. 2009). This agent should ONLY be prescribed by a consultant haematologist and ONLY when funding has been approved. Refer to the local chemotherapy protocol.

For all interferons, it is important to screen twice yearly for liver and thyroid disease, as well as surveillance for depression.

Busulfan
Refer to the local chemotherapy protocol. Busulfan is a historical treatment associated with a higher incidence of leukaemic transformation than treatment with hydroxycarbamide. Other serious complications are idiopathic pulmonary fibrosis and aplasia. Its use is limited to patients over 65 due to the associated risk of leukaemia. It is a second-line therapy in those patients refractory/intolerant to HU. Discuss with consultant haematologist.

Low-dose cytarabine
The dosing is as per the MRC AML14 trial 20mg given sc bd 14 days every 28 days. Discuss with consultant haematologist.

Azacitidine
Azacitidine has been used in some patients with success – 75mg/m² for seven days (or 5-2-2 regimen) is a suitable starting dose. This should be discussed with a consultant haematologist. This is an unlicensed indication for azacitidine and is not funded by NHS England.

Erythropoietin
Erythropoietin is only of limited use (Cervantes 2004). Discuss with consultant haematologist and pharmacy.

Haematopoietic stem cell transplantation (HSCT)
There is evidence that a limited number of patients may benefit from HSCT; most recently, reduced intensity transplants have shown provisional promising results (Hessling 2002). Refer patients at diagnosis, if they are a suitable candidate, for discussion and for consideration of HSCT once IR-2 risk or above and certain IR-1 risk patients, e.g. rising blast count. See Annex 6 for JACIE-accredited centres in the LCA.
Investigational agents

Other JAK2 inhibitors are in clinical trials, as are combinations of JAK2 inhibitors and pan-deacetylase inhibitors. JAK2 inhibitors have thus far demonstrated significant and sustained improvement in splenomegaly, disease-related symptoms, functioning and quality of life. They have been well tolerated with minimal toxicities.

7.4. Fertility

Management protocols for women in pregnancy and in the three months before conception are more complex and individualised. These cases should be discussed with a consultant haematologist experienced in such cases.

For young patients with MPN due to undergo AML induction-type chemotherapy and/or an HSCT, the options for fertility preservation should be discussed and the patient referred to a fertility specialist for preservation of sperm and ovarian tissue or fertilised embryos.

Expert onco-fertility advice should be considered in line with the LCA guidance and recommendations for referral to fertility services.
8. Supportive Care

8.1. Anaemia

Red cell transfusions may be required in addition to dose-modification of cytoreductive medication(s) (see also Table 4).

8.2. Haemostasis and thrombosis

For thrombotic events, anticoagulate as per local protocols and ensure counts are well controlled to prevent future events. For prophylaxis, see each specific disease entity.

8.3. Hyperviscosity syndrome

Urgent platelet apheresis or red cell apheresis can be undertaken if high counts are causing symptoms of hyperviscosity. Cytoreductive therapy must be initiated or optimised simultaneously.

8.4. Infection

Local protocols should be followed for treatment of infections and prophylaxis.

8.5. Pain management

For symptomatic splenomegaly, see section 7: Treatment for disease-specific treatment options (hydroxycarbamide vs surgery vs splenic irradiation vs ruxolitinib or other chemotherapy in MF).

People reporting pain should be considered for non-pharmacological intervention including, but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.

8.6. Other symptom control

Table 4: Symptomatic therapy for MF

<table>
<thead>
<tr>
<th>Clinical need</th>
<th>Drugs/Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Danazol</td>
</tr>
<tr>
<td></td>
<td>ESA if EPO level &lt;125IU</td>
</tr>
<tr>
<td></td>
<td>Transfusion</td>
</tr>
<tr>
<td></td>
<td>Thalidomide + steroids (unlicensed indication)</td>
</tr>
<tr>
<td></td>
<td>Pomalidomide negative clinical trial (unlicensed indication)</td>
</tr>
<tr>
<td>Symptomatic splenomegaly</td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td></td>
<td>Hydroxycarbamide</td>
</tr>
<tr>
<td></td>
<td>Cladribine, others</td>
</tr>
<tr>
<td></td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Extramedullary haematopoiesis</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td></td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td>Risk of thrombosis or recurrence</td>
<td>Low-dose ASA</td>
</tr>
<tr>
<td></td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Clinical need</td>
<td>Drugs/Intervention</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Constitutional symptoms/QoL</td>
<td>Ruxolitinib and consider bisphosphonates for bone pain</td>
</tr>
<tr>
<td>Risk of leukaemia transformation</td>
<td>None specifically directed</td>
</tr>
<tr>
<td>Improved survival</td>
<td>Ruxolitinib, Allogeneic HSCT</td>
</tr>
</tbody>
</table>

8.7. Breathlessness

- Any inpatient showing signs of respiratory distress should be assessed by a physician with knowledge of treatment for patients with MPN and, if appropriate, referred for respiratory physiotherapy assessment in accordance with local on-call guidelines, unless of overt metabolic cause.
- Any patient showing signs of non-acute breathlessness should be assessed by a physician with knowledge of treatment for patients with MPN. Referral for respiratory physiotherapy assessment and intervention should always be considered.
- Ongoing breathlessness management strategies can be provided by occupational therapy or physiotherapy.

8.8. Weight loss

- A screening tool for the assessment of dietary issues should be completed weekly for inpatients and, if issues are identified, a referral should be made to a specialist dietitian.
- Referral for specialist dietetic input should be made in the following instances:
- Any patient with neutropenia should be provided with information and education on the neutropenic diet and be referred to a specialist dietitian.
- If artificial feeding is being considered, a referral to the specialist dietitian should be made.
- Any patient with mucositis should be referred for dietetic assessment, as well as for specialist speech and language assessment.
- Weight loss/malnutrition should be identified through weekly screening of inpatients.

8.9. Complex symptom management

Discuss with specialist palliative care team for advice on symptom management, e.g. pain, mucositis when there is no/poor response to standard interventions. If appropriate, referral can be made to the specialist palliative care team (see Appendix 7 for LCA referral form to specialist palliative care).
9. Treatment Summary and Care Plan

Patients with MPN are followed for life or have supervised care by a haematologist experienced in such disorders. The MDT outcome form and clinic letters will serve to communicate new lines of treatment/change of treatment with the GP.

Treatment summaries should therefore be agreed when there are any significant changes in treatment and follow-up plans. HNAs should be offered through follow-up, with a care plan completed to document the plans to address the issues raised by the patient.

9.1. Treatment summary and care plan

There are two related but distinct documents which patients should be given when there are changes in treatment:

- A treatment summary provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information (see Appendix 6: NCSI Treatment Summary).

- A care plan is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

Recommendation: An end of treatment consultation should be offered to every patient when there are any significant changes in treatment and follow-up arrangements. This should include an HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.
10. Follow-up Arrangements

Monitoring of blood counts and renal and liver function should occur according to treatment regimen and patient risk factors by practitioners experienced with these drugs. Telephone and/or nurse-led clinics or prescribing with agreement of the GP (using formalised protocols) may also be used for those patients who are stable and reliable (Appendix 5).

11. Rehabilitation and Survivorship

Patients with MPN are followed lifelong on treatment within, or supervised by, specialist haematology departments. Rehabilitation and survivorship issues should be monitored throughout the patient pathway and highlighted to the appropriate allied health professional, if required.

Survivorship issues can relate to the effects of the disease process and/or management of long-term adverse effects of treatment, including long-term monitoring/decisions about intermittent cessation of therapy. The LCA Survivorship Guidelines may provide some information.

Any patient experiencing or reporting reduced mobility and/or ability to perform activities of daily living should be referred for occupational therapy and physiotherapy assessment.

12. Research/Clinical Trials

The LCA has produced a directory of clinical trials that are actively recruiting patients with MPN. Please refer to the LCA website (www.londoncanceralliance.nhs.uk/trials) for the most up-to-date list.
13. End-of-life Care

For older patients and in those with high-risk disease, discussions regarding prognosis and treatment options should also include discussions on end-of-life care. These are to facilitate transitions between active disease-modifying therapy and clinical trials, to supportive care only at the time of disease progression/non-response. Care may be required from specialist palliative care teams which are available in all the cancer centres and units affiliated to the LCA.

To support consideration of referral to specialist palliative care, please refer to the LCA Referral Criteria for Specialist Palliative Care (see Appendix 8). The LCA form for referral to specialist palliative care can be found in Appendix 7: LCA Specialist Palliative Care Referral Form.

The named CNS/key worker, patient, family members and palliative care teams, as well as members of the inpatient ward team, may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

14. Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer; further details on these datasets are available in Annex 7. In line with peer review requirements, the LCA Haemato-Oncology Pathway Group and the LCA Clinical Board review this data on a regular basis to ensure all patients receive treatments intended to provide the best possible outcomes, consistent across all MDTs.
References


Annex 1: LCA Acute Leukaemias and Myeloid Neoplasms BMAT Diagnostics Summary Chart

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>AT DIAGNOSIS</th>
<th>RESTAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirate (NPH)</td>
<td>Immuno (RMH) EDTA (purple)</td>
</tr>
<tr>
<td>AML/AUL/MPL</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>APML</td>
<td>YES</td>
<td>YES (PML-RARA)</td>
</tr>
<tr>
<td>Ph+ AML or ALL</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ALL/Burkitt lymphoma</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>MDS (If ?AML/blasts on film, follow AML guide)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>MPN</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>CML (If ?AML/blasts on film, follow AML guide)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Cytopenias/Macrocytosis</td>
<td>YES</td>
<td>ONLY IF AML/LYMPHOMA SUSPECTED</td>
</tr>
</tbody>
</table>

KGC = Kennedy Galton Regional Centre for Cytogenetics (located at NPH site, St. Mark’s Level 8; x3104)  
GST = Guy’s & St Thomas’ Hospital (call when send; 020 7188 7188, ext 51060)  
ICHNT = Imperial College Healthcare NHS Trust (020 8383 2179/2167/2177)  
TDL = The Doctors Laboratory (Pathology Laboratory at LNWH)  
RMH = Royal Marsden Hospital (020 8722 4221)  
A = Aspirate  
I = Immunophenotyping  
C = Cytogenetics  
M = Molecular  
T = Trephine  
TS = Trial Sample  
? = Ask Trial Coordinators
Annex 2: Multidisciplinary Teams (MDTs) and Constituent Hospital Trusts

<table>
<thead>
<tr>
<th>South East London MDT 1</th>
<th>Guy’s &amp; St Thomas’ NHS Foundation Trust/Lewisham and Greenwich NHS Trust (Lewisham Hospital and Queen Elizabeth Hospital)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South East London MDT 2</td>
<td>King’s College Hospital NHS Foundation Trust (including Princess Royal University Hospital)</td>
</tr>
<tr>
<td>South West London MDT 1</td>
<td>Kingston Hospital NHS Foundation Trust/St George’s University Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td>South West London MDT 2</td>
<td>Epsom and St Helier University Hospitals NHS Trust/Croydon Health Services NHS Trust</td>
</tr>
<tr>
<td>South West London MDT 3</td>
<td>The Royal Marsden NHS Foundation Trust</td>
</tr>
<tr>
<td>North West London MDT 1</td>
<td>Imperial College Healthcare NHS Trust/The Hillingdon Hospitals NHS Foundation Trust/Chelsea and Westminster Hospital NHS Foundation Trust/West Middlesex University Hospital NHS Trust/Ealing Hospital</td>
</tr>
<tr>
<td>North West London MDT 2</td>
<td>The London North West Healthcare NHS Trust (Northwick Park Hospital and Central Middlesex Hospital)</td>
</tr>
</tbody>
</table>
## Annex 3: LCA Oral Chemotherapy Patient Education Checklist

### Oral anti-cancer patient and carer education checklist

**Prior to first cycle:**

*This checklist must be completed with the patient/carer at the point of handing the medication to the patient, either in conjunction with or following a pre-treatment consultation.*

<table>
<thead>
<tr>
<th>Instructions for taking</th>
<th>Tick if discussed with the patient/carer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain how and when to take the medicine, including any treatment breaks.</td>
<td></td>
</tr>
<tr>
<td>If the patient is unable to swallow tablets or capsules or has a feeding tube, please refer to the oral systemic anti-cancer therapies (SACT) counselling handbook to dissolve or open capsules (if appropriate for the oral anti-cancer medicine).</td>
<td></td>
</tr>
<tr>
<td>Missed doses can be taken if near to the scheduled time. Otherwise, do not try and catch up or double the next dose. Wait until the next dose is due.</td>
<td></td>
</tr>
<tr>
<td>In case of vomiting after taking a dose, do not repeat the dose. Take the next dose at the normal time. If this occurs again, contact the chemotherapy team/24-hour advice line.</td>
<td></td>
</tr>
<tr>
<td>Check that the patient is aware of side effects and has received written information. Any side effects should be reported to your chemotherapy nurse or doctor.</td>
<td></td>
</tr>
<tr>
<td>If the patient is taking any prescribed/over-the-counter medicine/supplement – the patient should inform their medical team.</td>
<td></td>
</tr>
<tr>
<td>Return any unused oral anti-cancer medicine to the hospital pharmacy. Do not flush or throw them away (for high-cost drugs see the counselling handbook).</td>
<td></td>
</tr>
</tbody>
</table>

### Storage and handling

- The oral anti-cancer medicine should not be handled by anyone who is pregnant or planning a pregnancy (except on the advice of medical team).
- If the carer is giving the anti-cancer medicine, they should not handle the medicine directly but wear gloves or push the medicine out of the blister pack (if applicable) directly into a medicine pot.
- Store the tablets/capsules in the container provided.
- Store the tablets/capsules in a secure place, away from and out of sight of children.
- Wash hands thoroughly after taking/giving the oral anti-cancer medicine.
- Check that the patient understands how to take the treatment, by asking them to repeat back their instructions.
**Written information provided**

<table>
<thead>
<tr>
<th>Written information provided</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Taking an oral anti-cancer medicine’ patient information sheet</td>
<td></td>
</tr>
<tr>
<td>Diary for taking your oral anti-cancer medicine (if applicable)</td>
<td></td>
</tr>
<tr>
<td>For swallowing difficulty only – give relevant factsheet if appropriate for the oral anti-cancer medicine and an oral anti-cancer pack with disposables (e.g. oral/enteral syringes)</td>
<td></td>
</tr>
<tr>
<td>Dissolving oral anti-cancer tablets safely</td>
<td></td>
</tr>
<tr>
<td>Opening oral anti-cancer capsules safely</td>
<td></td>
</tr>
<tr>
<td>Giving an oral anti-cancer medicine through a feeding tube</td>
<td></td>
</tr>
<tr>
<td>Giving an anti-cancer syringe by mouth</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient name</th>
<th>Counselling/educated by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital number</td>
<td>Pharmacist/Pharmacy technician/Nurse/Interpreter</td>
</tr>
<tr>
<td>Signature and date</td>
<td>Signature and date</td>
</tr>
</tbody>
</table>

**Before all subsequent cycles:**

Check that the patient has understood the checklist above and repeat if necessary.

Check that any side effects experienced with their previous cycle were discussed with their medical team.

If a dose adjustment has been made, check that the patient is aware why their dose has been changed and how many tablets/capsules they should now take.

Check that the patient had no problems taking their previous cycle.

Check that the patient understands how to take the treatment, by asking them to repeat back their instructions.

Please retain a copy and/or endorse the prescription/electronic patient record as evidence counselling took place at each cycle.
Annex 4: Nurse-led MPN Clinic SOP and Referral Guideline

[Polycythaemia vera (PV) and essential thrombocythaemia (ET)]

Background

The nurse-led MPN clinic is often established in response to a number of factors:

1. A growing number of patients in haematology clinics which can lead to lengthy waits.
2. To live with a chronic blood condition, patients require education and support, effectively provided by a clinical nurse specialist (CNS).
3. Nurse-led clinics are supported by recent government and nursing policy which encourages new collaborative ways of working across professional boundaries to make effective use of human and other resources (DH, 1999).

It is envisaged that the nurse-led clinic will enable consultant haematologists to see more complex patients, keeping clinics running in a more efficient and timely manner, and that patients will receive continuity of care and high-quality, multi-professional care.

Role of the haematology clinical nurse specialist

The role of the CNS in the clinic includes the following:

• Monitoring the patient’s condition in order to maintain disease stability and control. This involves taking a full history, physical assessment, interpreting blood results, and prescribing and management of medication.

• Educating and empowering patients by explaining the illness to them, their carers and families, assisting them to identify signs of deterioration and how to take appropriate action, and promoting increased compliance with medication.

• Psychological and emotional support/holistic care including referral to allied healthcare professionals as appropriate.

Potential advantages

Development of this nursing role improves the quality of the service provided for haematology patients (Scope of Professional Practice, 2010) and reduces workload pressures on junior and senior doctors.

Improvements anticipated as a result of implementing this service include:

• Provision of a more flexible service for patients with regards to appointments
• Rapid access to services and reduced waiting times
• Patients increasingly able to deal more effectively with health problems
• Patients’ holistic needs being met
• A more cost-effective service for the Trust
• CNS professional development.
The CNS has gained specialist experience in patients with MPNs through shadowing the doctors and running the clinic in parallel with the haematology consultant. CPD will be undertaken to increase CNS knowledge in the MPNs and other general haematology conditions and to develop clinical expertise. This will be achieved through the following:

- Attending relevant study days/courses/conferences
- Visits to/observation of specialist clinics at other centres
- Feedback to and from and discussion with medical and nursing colleagues
- Reflection
- Case studies and problem solving
- Professional portfolio
- Completing the extended nurse prescribing course.

**Indemnity**

Upon approval of this document and following competency assessment of the CNS by the consultant haematologist, the Trust will provide vicarious liability, providing practice is within written protocols. The Royal College of Nursing indemnity insurance will also cover the CNS.

**Accountability**

The haematology CNS will at all times adhere to the Nursing and Midwifery Council (NMC) Code of Professional Conduct (2010) and be professionally responsible and accountable for his/her own actions. The NMC makes it clear that the ultimate responsibility is upon the practitioner to determine his/her own individual competence and also to be prepared to refuse to undertake a task if he or she feels they are not competent to undertake it. The consultant haematologist will ultimately remain responsible for the medical management of the patient.

**Mode of referral to MPN nurse-led clinic**

Referral to the nurse-led clinic may be made by the consultant haematologist, associate specialist or specialist trainees working in haematology. The decision for referral to the clinic will be documented in the medical notes and an MPN nurse-led clinic referral form completed and given to the CNS. The haematology secretaries and administrative clerks are informed by the CNS or individual making the referral so that the patient’s name is added to the CNS clinic list.

**Criteria for patients to be included**

- Patients with PV or ET who are stable and asymptomatic on treatment (venesection, hydroxycarbamide, anagrelide or interferon).
- Patients with MPN who require support to manage their disease effectively.
- Patients in whom the disease progresses or who become unstable and therefore require medical intervention will be referred back to the consultant haematology clinic. All patients will be reviewed annually by a doctor for a physical assessment and to assess for hepatosplenomegaly. This can be done jointly in the nurse-led clinic.
Workload

The CNS can independently see a maximum of 10 patients in one clinic session. Time should be given for administrative work. The CNS should also be available to accompany consultants or SpRs in consultations with new or follow-up patients. The CNS should also be able to refer patients to other members of the multidisciplinary team. Some patients will be able to be monitored through a CNS-led telephone clinic.

Location and frequency

The nurse-led MPN clinic is held in the outpatient department. Frequency of the clinic depends on the patient population and catchment/need, but it should be run in parallel with the consultant clinic so that there is a doctor available to provide advice or see the patient and/or to prescribe medication as needed.

Liaising with doctors

In the event that the CNS needs medical advice about a patient or for the prescribing of medication, he/she liaises with a doctor in haematology. If further investigations are needed, this would be done after discussing the patient with the doctor.

Patients will be seen annually by the doctors for a medical review. The CNS will discuss the patient with the consultant haematologist if he/she is concerned about the patient, for example splenomegaly (e.g. early satiety or abdominal distension) etc.

The CNS will discuss all patients after clinic with the consultant in order to provide medical oversight. The CNS dictates a letter to the patient’s GP after each consultation and these letters are also co-signed by the patient’s consultant.

Medicines management

Many of these patients will be taking some form of treatment such as hydroxycarbamide, interferon, anagrelide or busulfan to control blood counts or symptoms of disease. Dose adjustments may be required according to blood results and clinical history. When the FBC is stable, the interval between appointment times may be increased to a maximum of four months. In this case, a blood test should be done at two months and the results checked by the CNS. The CNS will then call the patient and inform them of any dose adjustments if needed. If the platelet count is less than 200 on two consecutive occasions the CNS can reduce the dose of hydroxycarbamide. If the platelets are above 400 on two or more consecutive occasions the CNS can increase the dose of hydroxycarbamide. These dose adjustments should be considered alongside other blood results such as haemoglobin and neutrophils, etc.

The CNS will give advice on medications only when he/she is confident that he/she can do so with the same competence as a doctor professing to have that skill (Bolan, 1957). Dose adjustments will be communicated to the patient’s GP via a letter which will also be co-signed by the patient’s consultant.

Venesection

If a venesection is indicated (to keep haematocrit below a specific target), the CNS will liaise with haematology day care.
Documentation

Patient assessments, blood counts and advice given are documented in the medical notes and the electronic patient record. Information is also entered onto a database detailing the patient’s demographics and treatment details, which is constantly updated and modified. This is to help with future audits.

Sickness and annual leave cover

When the CNS is on annual leave or study leave, the clinic will be cancelled and patients will be rescheduled. In the event of sickness, the patients will be urgently accommodated into the consultant clinic.

Evaluation

Evaluation is the systemic, objective and critical assessment of the degree to which services fulfil their stated goals. It can be applied to the processes of care, the actual actions and behaviours of the staff giving the care, and the outcomes of care which refers to what is actually achieved in measurable terms.

Evaluation of the nurse-led clinic will aim to establish its effectiveness and benefit both to patients and to the delivery and outcomes of care. Such information will inform future service developments and will add to the evidence base regarding nurse-led clinics in general. The following will be evaluated:

1. Patient satisfaction with aspects of care such as waiting times, continuity of care, history taking and assessment, perception of nurses’ knowledge and information giving or advice sharing.

2. Impact on service delivery/organisation of services – sources of referral, number of patients seen, impact of waiting times, length of consultation and “what is it about the nursing that enhances care”.

3. Impact on nursing such as identification of training needs, impact on other role functions, number of referrals to others, number of prescriptions required, etc.

4. Audit – systematic and critical analysis reviewed against explicit criteria, allowing practice to be modified where indicated:
   a. Appropriate/inappropriate referrals
   b. Accuracy of treatment advice/dose adjustments
   c. DNA rates
   d. Analysis of complaints

References


Referral Form for MPN (PV/ET) Nurse-led Clinic

N.B. Only refer if the patient is on a stable dose of medication and has controlled counts. If the patient has active medical problems related to MPN, do not refer.

NAME (OR STICKER): _____________________________________________

HOSPITAL NUMBER: _____________________________________________

D.O.B: ________________

TYPE OF MPN (Please circle): PV  ET

DATE OF DIAGNOSIS: __________________________

HISTORY OF THROMBOTIC OR HAEMORRHAGIC EVENTS:

DIAGNOSTIC INVESTIGATIONS (Please give results):

PRESENTING FBC:   HB  G/L
                  PCV
                  WBC  x 10⁹/L
                  PLTS  x 10⁹/L

MUTATION STATUS:

ABDOMINAL EXAMINATION/ABDOMINAL USS (Give date):

RCM/PV: ________________     DATE: _______________________

BONE MARROW ASPIRATE AND TREPHINE (DATE):

OXYGEN SATURATIONS: ________________  BLOOD PRESSURE: ________________

OTHER INVESTIGATIONS:

TREATMENT (Circle):  HYDROXYUREA  ANAGRELIDE  INTERFERON

STABLE DOSE:

OTHER ISSUES:

NAME AND SIGNATURE OF REFERRING DOCTOR: _____________________________________________

DATE OF REFERRAL: ________________
Annex 5: SIHMDS or Current Diagnostic Services and Contacts

**Guy’s & St Thomas’ NHS Foundation Trust**
- Cytogenetics/Flow Lab
- ViaPath Pathology
- 4th Floor, Southwark Wing
- Guy’s Hospital
- Great Maze Street
- London, SE1 9RT

**For APML diagnostic and MRD**
- Dr Yvonne Morgan
- Molecular Oncology Diagnostics Unit
- GSTT Pathology, 4th Floor, Southwark Wing
- Guy’s Hospital
- Great Maze Street
- London, SE1 9RT

**Imperial College Healthcare NHS Trust**
- Imperial Molecular Pathology Laboratory
- G Block, North Corridor
- Hammersmith Hospital
- Du Cane Road
- London, W12 0HS

**King’s College Hospital NHS Foundation Trust**
- KingsPath: Clinical Diagnostic Pathology Service
- Haematological Medicine
- King’s College Hospital
- Denmark Hill
- London, SE5 9RS

**London North West Healthcare NHS Trust**
- Processed centrally in TDL laboratories on-site for SIHMDS (in progress), cytogenetics/molecular to:
- North West Thames Regional Genetics Service, Haematology Section
- Northwick Park Hospital
- Watford Road
- Harrow, HA1 3UJ

**The Royal Marsden NHS Foundation Trust**
- The Centre for Molecular Pathology
- Downs Road
- Sutton, SM2 5PT
- Tel: 020 8915 6570
- Immunophenotyping Tel: 020 8915 6517 or 020 8915 6518
- Cytogenetics Tel: 020 8722 4232
- Molecular Genetics Tel: 020 8915 6565
Annex 6: JACIE-accredited Transplant Centres in the LCA

Imperial College Healthcare NHS Trust
Dr Eduardo Olavarria
Consultant Haematologist
BMT Programme Director
Haematology Department
ICHNT
Hammersmith Hospital
Du Cane Road
London, W12 0HS
Tel: 020 8383 3237
Fax: 020 8742 9335
Email: eduardo.olavarria@imperial.nhs.uk

Royal Marsden NHS Foundation Trust
Dr Mike Potter via 020 8661 3670
katrina.sharpe@rmh.nhs.uk
Dr Chloé Anthias, contact details as above.
Dr Mark Ethell, via 020 8661 3794,
PA: janet.bromell@rmh.nhs.uk

Department of Haematology-Oncology
The Royal Marsden NHS Foundation Trust
RS11, 2nd Floor, Orchard House,
Downs Road, Sutton,
Surrey, SM2 5PT
Tel: 020 8661 3670
Fax: 020 8642 9634 (safe haven)
Alternative email: katrina.sharpe@nhs.net

St George’s University Hospitals NHS Foundation Trust
Dr Mickey Koh
Director: Stem Cell Transplantation
Consultant Haematologist
St George’s Hospital and Medical School
Jenner Wing Corridor 6
Blackshaw Road
London, SW17 0QT
Tel: 020 8725 3545
Fax: 020 8725 2859
Email: mickey.koh@stgeorges.nhs.uk

King’s College Hospital NHS Foundation Trust
Bone Marrow Transplant Team
4th Floor, Hambleden Wing
King’s College Hospital
Denmark Hill
London, SE5 9RS
Tel: 020 3299 4694, 020 3299 5268
Annex 7: Data Requirements

Haematology oncology services within the LCA are required to submit data to the following nationally mandated datasets for all patients diagnosed with haematological cancers.

The Cancer Outcomes and Services Dataset (COSD)

The core dataset for all tumour types including haematological cancers is mandated from January 2013, and the site-specific dataset is mandated from July 2013. Details of the dataset can be found on the National Cancer Intelligence Network website:


The local cancer registry will be collating this dataset using Trust data feeds which should include all these items. The feeds are:

- Trust PAS
- Trust pathology
- Trust radiology
- Trust multidisciplinary team (MDT) feed.

In line with the requirements set out in Provider Trust contracts, this data should be submitted within 25 workings days of the end of the month in which the activity took place.

<table>
<thead>
<tr>
<th>Three groups of haematological cancers are considered stageable by the Registry:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lymphomas, using Ann Arbor (or Murphy St Jude for children)</td>
</tr>
<tr>
<td>• Myelomas, using ISS</td>
</tr>
<tr>
<td>• CLLs, using Rai and Binet</td>
</tr>
</tbody>
</table>

For the purposes of COSD, any other haematological cancers are not counted as stageable.

| For CLL both Rai (0-IV) and Binet (A-C) stages need to be recorded and submitted to COSD to be considered “fully staged” |

MGUS does not need to be recorded and submitted as it is not defined as an invasive tumour.

Systemic Anti-Cancer Therapy dataset (SACT)

Provider Trusts that provide chemotherapy to patients are required to submit data to the SACT dataset. Details of the audit and the dataset requirements are available on the dataset homepage:

www.chemodataset.nhs.uk/home.aspx
Radiotherapy Dataset (RTDS)

Provider Trusts that provide radiotherapy to patients are required to submit data to the RTDS dataset. Details of the audit and the dataset requirements are available on the dataset homepage:
http://www.canceruk.net/rtservices/rtds/

Cancer Waiting Times dataset

Trusts are required to submit data to the Cancer Waiting Times dataset, which includes details of all patients who are referred as a 2 week wait (2ww) referral, and all patients who are treated for cancer. Trusts are required to submit this data within 25 working days of the month of either when the patient was first seen for the 2ww target, or when the patient was treated. The cancer waiting times dataset can be found at:

Local data requirements

The LCA Haematology Oncology Pathway group is working on developing a suite of metrics to inform the group and services within the LCA on areas of priority and potential service improvement. The LCA is currently collating information which is available through sources of data currently available, though the Haematology Oncology Pathway Group or LCA clinical board may require Trusts to submit additional MDT data to the LCA if additional priority areas are identified.
Appendices

Appendix 1: 2 Week Wait Referral Forms
  - North West London
  - South East London
  - South West London

Appendix 2: Treatment of Children

Appendix 3: Treatment of Teenagers and Young Adults
  - Teenagers and Young Adults PTC Referrals
  - Teenagers and Young Adults MDT Proforma

Appendix 4: LCA Key Worker Policy

Appendix 5: LCA Holistic Needs Assessment Tool

Appendix 6: NCSI Treatment Summary

Appendix 7: LCA Specialist Palliative Care Referral Form

Appendix 8: LCA Referral Criteria to Specialist Palliative Care