Hull University Teaching Hospitals NHS Trust

Hull University Teaching Hospitals and North Lincolnshire NHS Trusts

Haematology Multidisciplinary Team Guideline and Pathway

Myeloproliferative Neoplasms Guideline

1 BACKGROUND

The Hull and North Lincolnshire Haematology Multidisciplinary team manages patients with haematological malignancies on three sites, Diana Princess of Wales Hospital Grimsby, the Queens Centre for Haematology and Oncology at Castle Hill Hospital Hull University Teaching Hospital NHS Trust and Scunthorpe Hospital.

Levels of service provided in these organisations is as defined in the NICE guidance "Haematological Cancers: improving outcomes NG47" 25th May 2016.

Low-to-intermediate intensity chemotherapy is delivered in Grimsby, the Queens Centre Castle Hill Hospital and Scunthorpe Hospital.

Low-to-intermediate intensity chemotherapy, high-intensity chemotherapy and autologous stem cell transplantation is delivered at the Queens Centre, Castle Hill Hospital.

Allogeneic stem cell transplantation is delivered in the regional transplant centres in Leeds, Nottingham and Sheffield.

Anagrelide, low dose busulphan, hydroxycarbamide, interferon and ruxolitinib will be delivered in sites offering low-to intermediate intensity chemotherapy.

2 POLICY / PROCEDURE / GUIDELINE DETAIL

The Hull and North Lincolnshire MDT has decided that patients with Myeloproliferative neoplasms (MPN) will be managed in line with the MPN British Committee for Standards in Haematology (BCSH) and European LeukemiaNet (ELN) guidelines:-

- Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol. 2010 May;149(3):352-75.
- Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations from European LeukemiaNet. J Clin Oncol. 2011 Feb 20;29(6):761-70.
- Modification of British Committee for Standards in Haematology diagnostic criteria for essential thrombocythaemia. Br J Haematol. 2014 Nov;167(3):421-3.
- Use of JAK inhibitors in the management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and Management of Myelofibrosis 2012. Br J Haematol. 2014 Nov;167(3):418-20.
- A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. Br J Haematol. 2019 Jan;184(2):176-191.

The local management of MPN will also take account of the following NICE guidance:-
Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis. Technology appraisal guidance (TA386). Published date: 23 March 2016.

3. GUIDELINE

This guideline covers the diagnosis and management of the MPNs:-

1. Polycythemia Vera (PV).
2. Essential Thrombocythaemia (ET).
3. Primary Myelofibrosis (PMF).

Mutations in PV, ET, and PMF

- PV – 100 % JAK-2 mutations (Exon 14 or 12).
- ET – 60-65 % JAK-2 mutation, 20-25 % CALR mutation, 3 % MPL mutation.
- PMF – 60-65 % JAK-2 mutation, 20-25 % CALR mutation, 7 % MPL mutation.

Complications of MPN's

- Thrombosis.
- Bleeding.
- Transformation to Acute leukemias.
- Extra medullary haematopoiesis.

POLYCYTHAEMIA VERA

Recommended diagnostic criteria for PV
JAK2-positive polycythaemia vera (requires both criteria)
A1 High haematocrit (>0·52 in men, >0·48 in women) OR raised red cell mass (>25% above predicted)
A2 Mutation in *JAK2*
JAK2-negative polycythaemia vera (requires A1-A4 plus another A or two B criteria) *
A1 Raised red cell mass (>25% above predicted) OR haematocrit ≥0·60 in men, ≥0·56 in women
A2 Absence of mutation in *JAK2*
A3 No cause of secondary erythrocytosis
A4 Bone marrow histology consistent with polycythaemia vera
A5 Palpable splenomegaly
A6 Presence of an acquired genetic abnormality (excluding *BCR-ABL1*) in the haematopoietic cells
B1 Thrombocytosis (platelet count >450 × 10^9/l)
B2 Neutrophil leucocytosis (neutrophil count >10 × 10^9/l in non-smokers, ≥12·5 × 10^9/l in smokers)
B3 Radiological evidence of splenomegaly
B4 Low serum erythropoietin

Table 1. Diagnostic criteria for polycythaemia. From Br J Haematol. 2019 Jan;184(2):176-191.

Additional investigations:

- JAK2 exon 12
- Consider further genetic testing by next generation sequencing if young onset/positive family history
- Bone marrow biopsy

Management Of Polycythaemia Vera

Low Risk PV **(<60 years, No Previous Thrombotic episode, No Cardiovascular risk factors, normal white cell count)**	**High Risk PV** **(>60 years,Previous Thrombotic episode, Presence of Cardiovascular risk factors, raised white cell count)**
Venesection to maintain the Hct < 0.45	Venesection to maintain the Hct < 0.45
Low-dose aspirin	Low-dose aspirin
Assessment and management of cardiovascular risk factors (blood pressure control, weight loss, physical activity and counselling to stop smoking)	Cytoreductive therapy
Pruritus: Ranitidine, Cetirizine, Fexofenadine	

Cytoreduction should be considered if:-

- High Risk PV.
- Poor tolerance of venesection.
- Symptomatic or Progressive splenomegaly.
- Other evidence of disease progression, e.g. weight loss, night sweats.
- Thrombocytosis / Leucocytosis/erythromelalgia.

Choice of cytoreductive therapy, if indicated:-

< 40 years	40-75 Years	> 75 years
First line: Interferon	**First line:** Hydroxycarbamide,	**First line:** Hydroxycarbamide
Second line: Hydroxycarbamide or Anagrelide	**Second line:** Interferon or Anagrelide	**Second line:** P32 or intermittent low dose busulphan.

ESSENTIAL THROMBOCYTHAEMIA

Diagnosis requires A1–A3 or A1 + A3–A5	
A1	Sustained platelet count ≥450 × 10^9/l
A2	Presence of an acquired pathogenetic mutation (e.g. in the *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)

Table 2. Investigation of thrombocytosis from Br J Haematol. 2010 May;149(3):352-75.

Additional investigations:-

- MPL exon 10.
- BCR-ABL1 if there are atypical features eg. Basophilia.
- Bone marrow biopsy with cytogenetics.

Management Of Essential thrombocythaemia

<table>
<tr><td>High Risk

Any of the following: Age>60, Platelet count >1500, Previous thrombosis, Raised wbc count, Cardiovascular risk factors, haemorrhagic symptoms related to ET</td><td>Intermediate Risk

All of the following: Age 40-59, Platelet count <1500, No cardiovascular risk factors, No previous thrombosis, Normal white cell count, no haemorrhagic symptoms related to ET</td><td>Low Risk

All of the following: Age<40, Platelet count <1500, No cardiovascular risk factors, No previous thrombosis, Normal white cell count, no haemorrhagic symptoms related to ET</td></tr>
<tr><td>1. Aspirin</td><td colspan="2">1. Aspirin</td></tr>
<tr><td>2. Cytoreduction :

1st line - Hydroxycarbamide (Interferon in patients < 40)

2nd line - Anagrelide

Interferferon alpha.

P32/Low dose Busulphan in patient >70.</td><td colspan="2">2. Cytoreduction:

if patient symptomatic with splenomegaly, erythomelalgia

microvascular complications not improved on aspirin

if patient has uncontrolled bleeding with high platelet count</td></tr>
<tr><td colspan="3">3. Manage reversible vascular risk factors</td></tr>
</table>

Other management considerations

Consider relaxing platelet target to 400-600 x 10^9/L in patients who are intolerant/resistent to cytoreductive therapy.

Managing ET in special circumstances including pregnancy and splanchnic vein thrombosis should be as part of a multidisciplinary team and in line with BCSH guidelines.

MYELOFIBROSIS

Diagnosis requires A1 + A2 and any two B criteria	
A1	Bone marrow fibrosis ≥3 (on 0–4 scale)
A2	Pathogenetic mutation (e.g. in *JAK2*, *CALR* or *MPL*), or absence of both *BCR-ABL1* and reactive causes of bone marrow fibrosis
B1	Palpable splenomegaly
B2	Unexplained anaemia
B3	Leuco-erthroblastosis
B4	Tear-drop red cells
B5	Constitutional symptoms*
B6	Histological evidence of extramedullary haematopoiesis

*Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37·5°C) or diffuse bone pains.

Table 3. Primary myelofibrosis (requires A1 + A2 and any two B criteria) from Br J Haematol. 2014 Nov;167(3):418-20.

A1	Bone marrow fibrosis ≥3 (on 0–4 scale)
A2	Previous diagnosis of ET or PV
B1	New palpable splenomegaly or increase in spleen size of ≥5 cm
B2	Unexplained anaemia with 20 g/l decrease from baseline haemoglobin
B3	Leuco-erythroblastic blood film.
B4	Tear-drop red cells
B5	Constitutional symptoms*
B6	Histological evidence of extramedullary haematopoiesis.

*Drenching night sweats, weight loss >10% over 6 months, unexplained fever (>37·5°C) or diffuse bone pains.

Table 4. Post-ET/PV myelofibrosis (requires A1 + A2 and any two B criteria) from Br J Haematol. 2014 Nov;167(3):418-20.

Additional investigations:

PDGFRA/B mutation should be excluded if a significant and persistent eosinophilia is present.

Risk stratification with DIPSS and DIPSS-Plus score should be done at diagnosis and on reassessment and should be used to make therapeutic decisions.

High risk mutations (ASXL, SRSF2, IDH, EZH2 and U2AF) offer prognosis information independent of the DIPSS plus score

Management Of Myelofibrosis

Low Risk Disease	**Intermediate /High Risk Disease**
Active monitoring **Symptom-directed therapy +/- Myelosupression:** **1. Splenomegaly:** • Hydroxycarbamide • Ruxolitinib • Interferon • Radiotherapy • Splenectomy **2. Anaemia** • Transfusion • Erythropoietin (if Epo < 125mU/ml) • Androgens (Danazol) • Thalidomide • Prednisolone **3. Consitutional Symptoms** • Ruxolitinib • Hydroxycarbamide • Fexofendine for pruritus **4. Localised bone pain/symptomatic extramedullary haematopoiesis** • Involved field radiotherapy	**Ruxolitinib** **Allogenic SCT** • Int-2/High risk disease age<70 • Int-1 age <65 if either refractory, transfusion dependent or adverse cytogenetics

Assessment and monitoring

All new MPN patients are discussed at MDT and reviewed thereafter in the Consultant-led face-to-face clinic. Those patients deemed to have stable disease can then be managed as part of the MPN remote review clinic.

It is advised that all MPN patients be regularly assessed using the MPN Symptom assessment form total symptom score (MPN-SAF TSS). This has been shown to be useful in making therapy decisions, assessing response to treatment and determining disease progression as well as informing regarding prognosis and survival.

3 PROCESS FOR MONITORING COMPLIANCE

Compliance will be audited within the MDT audit programme.

4 REFERENCES

- Hull and North Lincolnshire Haematology MDT operational policy September 2019.
- Haematological cancers: improving outcomes. NICE guideline [NG47] Published date: May 2016.
- Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol. 2010 May;149(3):352-75.
- Philadelphia-Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations from European LeukemiaNet. J Clin Oncol. 2011 Feb 20;29(6):761-70.
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