Clinical Guidelines for Leukaemia and other Myeloid Disorders – Myeloproliferative Neoplasms

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Version History

Version	Date Issued	Brief Summary of amendments	Owner's Name:
1			Dr
2		Chronic Myeloid Leukaemia updated Polycythaemia Vera wording updated	Dr Sebastian Francis
3	11/05/18	Clinical study in CML and Clinical studies in PRV, ET, MF added	Dr Sebastian Francis
4	17/05/2019	New PRV Guidelines	Dr Sebastian Francis

(Please note that if there is insufficient space on this page to show all versions, it is only necessary to show the previous 2 versions)

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OUTLINE MANAGEMENT FOR PH+VE CHRONIC MYELOID LEUKAEMIA

Definitions of disease:

WHO Criteria for Chronic Phase

- Blasts <10% in bone marrow and peripheral blood
- Peripheral basophils <20%
- Not meeting criteria for AP/BC

WHO criteria for Accelerated Phase:

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

Criteria for Blast Crisis

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

Investigations at Diagnosis

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

Diagnostic samples:

Morphology
Peripheral blood film
Diagnostic Bone Marrow (if blood film morphology equivocal)
Aspirate (assess blast %)
Trephine

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

Molecular genetics
EDTA peripheral blood sample x2

a. Characterization of bcr-abl fusion breakpoint

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

Prognostic scoring systems

Sokal score (low/intermediate/high)
EUTOS score

Treatment (1st line)

NICE guidance

Imatinib

Imatinib 400mg daily is recommended as an option for untreated, chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults**.** Imatinib is recommended as an option for the treatment of people with Philadelphia-chromosome-positive CML who initially present in the accelerated phase or with blast crisis.

Nilotinib

Nilotinib 300mg bd is recommended, within its marketing authorisation, as an option for untreated chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults.

Dasatinib

Dasatinib 100mg daily is recommended, within its marketing authorisation, as an option for untreated chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults.

Consider Nilotinib in newly diagnosed females of childbearing age (nilotinib achieves deeper responses faster).

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

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

Definitions of response to therapy

Complete Haematological Response

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

Cytogenetic response (FISH on PB cells can be used instead of BM)

- *Complete 0% Ph+ve cells (>20 marrow metaphases)
- Partial 1-35%
- Minor 36-65%
- Minimal 66-95%
- None >95%

*Patients who achieve complete cytogenetic response should have their on going response to therapy monitored by serial bcr-abl/abl ratio testing.

Molecular Response

- Complete - Bcr-abl not-detectable
- Major <0.1% (i.e. >3 log reduction in bcr-abl/abl ratio).

Loss of response

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

Monitoring Therapy

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

During treatment:
-RQ-PCR every 3 months until MMR has been achieved and then every 3-6 months

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

Mutation analysis:
-failure to achieve milestones, rising BCRABL or loss of CCR

Response definitions for any TKI first line, and 2nd line in case of intolerance (as per ELN criteria)

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL^{IS} 1-10%* Ph+ 1-35%	BCR-ABL^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL^{IS} ≤0.1%* (MMR)	BCR-ABL^{IS} 0.1-1%*	BCR-ABL^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

Optimal response	Best long-term outcome No indication for a change of treatment.
Failure	Patient should receive a different treatment to limit the risk of progression and death
Warning	Characteristics of disease and response to treatment require more frequent monitoring to permit timely changes in therapy, in case of treatment failure.

Key Points

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

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

Response at 12 months	**% of progression free survival at 42 months**
No CCyR	75%
<3 log reduction (CCyR)	90%
>3 log reduction (MMR)	98%

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

Criteria for consideration BMT opinion.

- Patients failing imatinib and another TKI (resistance)
- Patients intolerant of at least 2 TKI

Indications for second generation TK inhibitors

- Patients intolerant to Imatinib
- Patients who fail/resistant to Imatinib therapy
- The European LeukaemiaNet definition of Imatinib failure in chronic phase CML

Treatment (2nd line)

NICE guidance

Dasatinib and **nilotinib** are recommended as options for treating only chronic- or accelerated-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults, if: they cannot have imatinib, or their disease is imatinib-resistant.

Dasatinib is administered orally. The recommended starting dosage is 100 mg once daily in the chronic phase or 140 mg once daily in the accelerated and blast-crisis phase and treatment should continue until disease progression or until no longer tolerated by the patient.

Nilotinib is administered orally. The recommended starting dosage is 400 mg twice daily for imatinib-resistant or intolerant CML in the chronic phase and 400 mg twice daily in the accelerated phase and treatment should be continued as long as the patient continues to benefit.

Bosutinib

Bosutinib is recommended as an option for chronic, accelerated and blast phase Philadelphia chromosome positive chronic myeloid leukaemia in adults, when:

- they have previously had 1 or more tyrosine kinase inhibitor and
- imatinib, nilotinib and dasatinib are not appropriate

All patients require a kinase domain mutation analysis prior to starting second generation TKI if resistant to imatinib. If patient <65 then consider referral for allograft discussion if haematological toxicity with imatinib/2nd generation TKI.

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

Management of CML after second line treatment failure

-Ponatinib
-Refer for BMT discussion

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

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

High risk scores (>2.5) = use EBMT pre transplant risk assessment score

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

Score	**0**	**1**
Sokal risk group	Low	Intermediate or high
Neutropenia during Imatinib therapy	No	Yes
Institution of 2G-TKI>18 months after Imatinib failure	No	Yes
Best cytogenetics response on Imatinib (% Ph-positive cells)	<95%	>95%

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

Score	**0-1**	**2**	**3-4**
Complete cytogenetic remission	95.6%	50%	18.7%

Indications for 3rd generation TKI

Ponatinib

For the treatment of Chronic Myeloid Leukaemia (CML) in adult patients with chronic phase, accelerated phase, or blast phase CML who:
- Are resistant to dasatinib or nilotinib or,
- Who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate or
- Who have the T315I mutation

Relevance of BCR-ABL kinase domain mutations

Advanced phase patients:-

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

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

Management of intolerance to Imatinib

Supportive care and side effect management should be employed
If the patient is truly intolerant (grade3/4), options that may be considered include:-

- Nilotinib, Dasatinib or Bosutinib.

Pregnancy

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

References

Abruzzese E et al. Nilotinib in chronic myelogenous leukemia patients who fail prior imatinib and dasatinib therapy: updated results of an open-label phase II study. J Clin Oncol. 2008,26, 385

Quintas-Cardama A et al. Dasatinib (BMS-354825) is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib (AMN107) therapy failure. Blood 2007; 109, 497-9.

GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF POLYCYTHAEMIA VERA

Modified diagnostic criteria for polycythaemia vera (2018 BCSH Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis)

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 *JAK* 2

***JAK2*-negative polycythaemia vera (requires A1-A4 plus another A or two B criteria)**[a]

A1 Raised red cell mass (>25% above predicted) OR haematocrit ≥0·60 in men, ≥0·56 in women

A2 Absence of mutation in *JAK* 2

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

Treatment goals

- Reduce thrombosis and haemorrhage risk
- Minimise complications and symptomatology
- Minimise risk of transformation to myelofibrosis and acute leukaemia
- Manage specific situations such as pregnancy and surgery
- Achieve good haematocrit control to <0·45

Risk Stratification

- **Age and thrombotic history should be used to define risk groups for thrombosis in polycythaemia vera (PV)**
- **'High risk': age ≥65 years and/or prior PV-associated arterial or venous thrombosis**
- **'Low risk': age <65 years and no PV-associated thrombotic history**
- **Some 'low risk patients' may be to be considered at higher risk in the presence of cardiovascular risk factors, elevated white blood cell (WBC) count, extreme thrombocytosis or haematocrit (Hct) uncontrolled with venesection**

Management

Primary care:
Address risk factors such as DM, Hypertension, peripheral vascular disease and Hyperlipidaemia

Recommendations: management options for ALL PV including low-risk patients

- **Target haematocrit of <0·45 in all patients (GRADE 1A)**
- **Low dose aspirin (75–100 mg) in all patients (GRADE 1A)**
- **Targeted intervention to reduce cardiovascular risk factors**

Consider cytoreductive therapy in low-risk patients with:

- **History of treated arterial hypertension, ischaemic heart disease or diabetes mellitus**
- **Persistent leucocytosis (e.g. WBC count >15 × 10^9/l)**
- **Uncontrolled haematocrit (or poor tolerability of venesection)**
- **Extreme/progressive thrombocytosis (e.g. ≥ 1500 × 10^9/l) and/or haemorrhagic symptoms**
- **Progressive/symptomatic splenomegaly**
- **Uncontrolled or progressive disease-related symptoms, e.g. weight loss, sweats**

Recommendations: Management options in high-risk patients

- **First Line: hydroxycarbamide (HC) or interferon (preferably pegylated interferon)**
- **Second line: in patients treated with HC as first line, interferon as second line treatment, or, where treated with interferon as first line, recommend HC as second line treatment**
- **Consider pegylated interferon as second line in those patients who have had non-pegylated interferon first line and could not tolerate it**
- **Ruxolitinib second/third line in HC resistant or intolerant patients**

Third-line or further treatment options

- **Busulfan or ^{32}P or pipobroman in those with limited life expectancy.**
- **Anagrelide in combination with HC may be helpful in those where platelet control is difficult**

European LeukaemiaNet criteria for hydroxycarbamide intolerance and resistance

1. Need for phlebotomy to keep haematocrit <0·45 after 3 months of at least 2 g/day of hydroxycarbamide OR

2. Uncontrolled myeloproliferation, i.e. platelet count >400 × 10^9/l AND white blood cell count >10 × 10^9/l after 3 months of at least 2 g/day of hydroxycarbamide OR

3. Failure to reduce massive[a]
splenomegaly by more than 50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of hydroxycarbamide OR

4. Absolute neutrophil count <1·0 × 10^9/l OR platelet count <100 × 10^9/l OR haemoglobin <100 g/l at the lowest dose of hydroxycarbamide required to achieve a complete or partial clinico-haematological response OR

5. Presence of leg ulcers or other unacceptable hydroxycarbamide -related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of hydroxycarbamide.

DIAGNOSIS AND MANAGEMENT OF ESSENTIAL THROMBOCYTHAEMIA

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

JAK2-positive thrombocythaemia

A1 Platelet count >450
A2 Presence of an acquired pathogenetic mutation (eg in the JAK2 or CALR genes +CMPL)
A3 No other myeloid malignancy, especially PV[1], PMF[2], CML[3], MDS[4]
A4 No reactive cause for thrombocytosis and normal iron stores
A5 Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm. Reticulin is generally not increased

1-Excluded by a normal haematocrit in an iron replete patient
2-indicated by significant marrow bone marrow fibrosis and palpable splenomegaly, blood film abnormalities or unexplained anaemia
3-Excluded by absence of BCRABL1from marrow or PB
4-Excluded by absence of dysplasia on examination of blood film and bone marrow aspirate

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

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

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

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

- Age 40-59 years
- Platelet count $<1500^9$/l
- No history of ischaemia, thrombosis or embolic features or erythromelagia
- Absence of haemorrhage considered related to ET
- Absence of diabetes
- Absence of hypertension

High risk:
(Patients having any of the following features)

- Age $\geq$ 60 years
- Platelet count > 1500^9/l
- History of ischaemia, thrombosis or embolic features or erythromelagia
- Haemorrhage considered related to ET
- Presence of diabetes
- Presence of hypertension

Treatment options

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

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

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

Failure of hydroxycarbamide is defined as follows:-
(LeukaemiaNet definition of clinical resistance/intolerance to hydroxycarbamide in ET)

Platelet count > 600,000/ul after 3 months of at least 2g/day of hydroxycarbamide (2.5g/day in patients with body weight > 80kg).

Or

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

Or

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

Or

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

Or

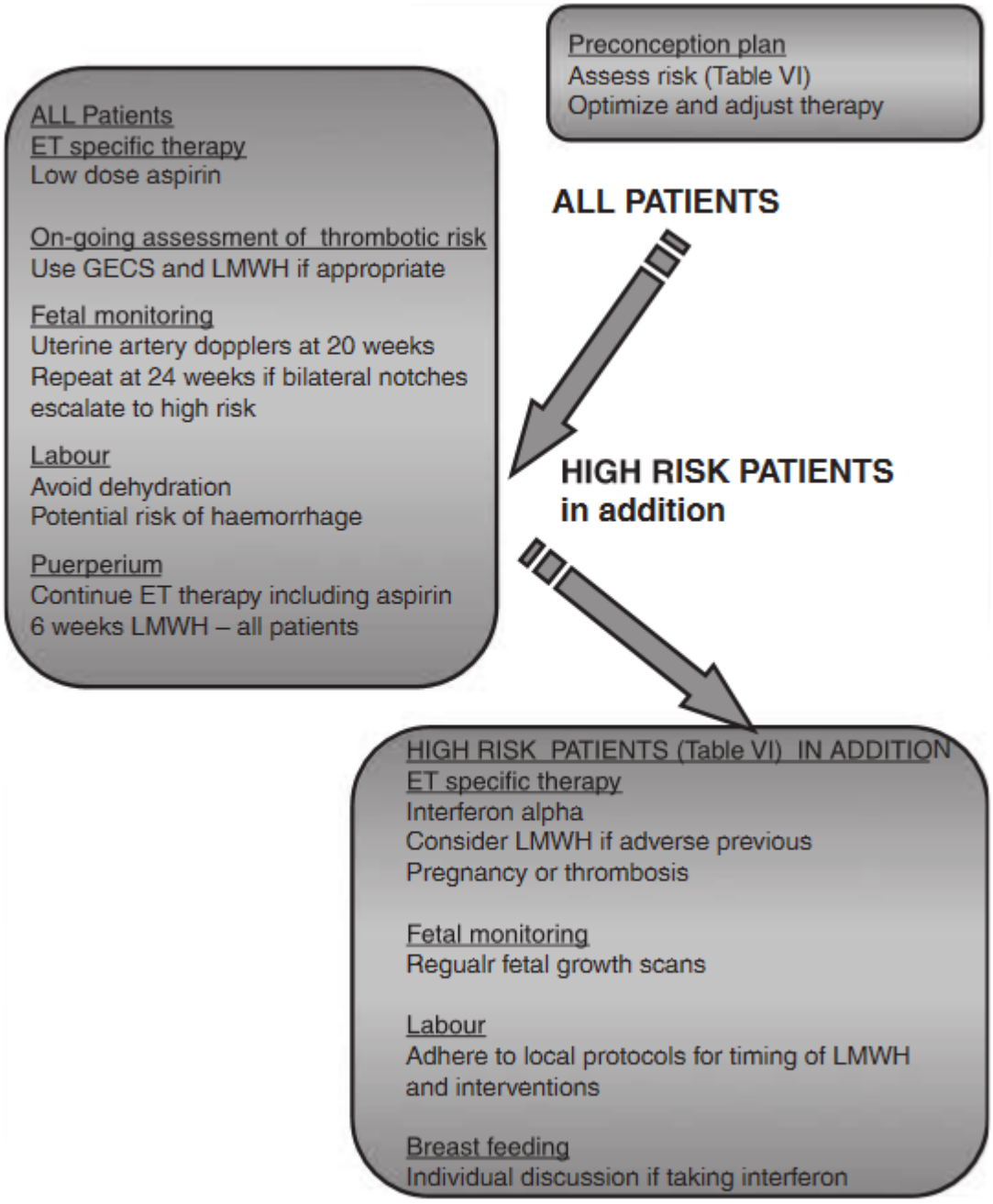
Hydroxycarbamide- related fever

Pregnancy and ET

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

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

Algorithm for pregnancy management in ET (as per BCSH 2010)



GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF IDIOPATHIC MYELOFIBROSIS

Diagnostic Criteria (BCSH 2015)

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

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

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

Prognostic Factors

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

Variable	IPSS	DIPSS
Age > 65 years	✓	✓
Constitutional symptoms	✓	✓
Haemoglobin <100 g/l	✓	✓
Leucocyte count > 25 × 10^9/l	✓	✓
Circulating blasts ≥ 1%	✓	✓
	1 point each	1 point each but Hb = 2

DIPSS-Plus: add 1 point to the DIPSS RISK GROUP* (low = 0; intermediate 1 = 1, intermediate 2 = 2 and high risk = 3) in addition for:
Platelet count <100 × 10^9/l
RBC transfusion need
Unfavourable karyotype +8, −7/7q−,i(17q),inv(3), −5/5q−, 12p−, 11q23 rearrangement

	IPSS		DIPSS		DIPSS-Plus	
Risk group	Predictors (*n*)	Median survival (years)	Predictors (*n*)	Median survival (years)	Predictors (*n*)	Median survival (years)
Low	0	11·3	0	Not reached	0	15·4
Intermediate-1	1	7·9	1 or 2	14·2	1	6·5
Intermediate-2	2	4·0	3 or 4	4	2–3	2·9
High	≥3	2·3	5 or 6	1·5	≥4	1·3

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

Treatment

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

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

Intermediate 2 /High risk DIPSS
-Patients with symptomatic splenomegaly or constitutional symptoms in primary myelofibrosis, post ET myelofibrosis or post essential thrombocythaemia myelofibrosis are eligible for **Ruxolitinib** (if platelets>50). Patients must have INT2/HIGH risk disease DIPSS score
-For objective monitoring of symptoms while on Ruxolitinib suggest using MPN-SAF

Allograft candidates (as per EBMT/ELN IWG)

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

References

BCSH Guidelines 2015: 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

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

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

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