Myeloproliferative neoplasms

2016

Myelofibrosis

Criteria of diagnosis:

◉Major criteria:

1-presence of megakyrocyte proliferation and atypia, usually accompanied by either reticulin&/or collagen fibrosis or, in the absence of significant reticulin fibrosis, the megakaryocyte must be accompanied by an increased BM cellularity characterized by granulocytic proliferation and often decreased erythropoisis.

2-Not meeting WHO criteria for PRV,CML,MDS or other myeloid neoplasm.

3-Demonstration of JAK2617 or other clonal marker(MPL515w), no evidence of BM fibrosis due to underlying inflammatory or other neoplastic diseases.

◉Minor criteria:

1-Leukoerythroblastic picture

2-Increase in LDH

3-Anemia

4-Plapable spleen.

or:

require A1+A2 and any 2B criteria

A1- bone marrow fibrosis >= 3(on 0-4 scales) .

A2- pathogenic mutation (JAK2,MPL) or absence of both BCR-ABL1 and reactive cause of BM fibrosis

B1- palpable splenomegaly

B2- unexplained anemia

B3- leukoerythroblastic blood film

B4- tear drop shape red cell

B5- constitutional symptoms

B6- histological evidence of extra medullary hematopoiesis

Criteria myelofibrotic transformation of ET or PRV

require A1+A2 and any 2B criteria

A1- bone marrow fibrosis >= 3(on 0-4 scales) .

A2- previous diagnosis of ET or PRV

B1- new palpable splenomegaly r increase size of spleen size of >=5cm

B2- unexplained anemia with 2g/dl decrease from base line hemoglobin

B3- leukoerythroblastic blood film

B4- tear drop shape red cell

B5- constitutional symptoms

B6- histological evidence of extra medullary hematopoiesis

Scoring system:

Lille Scoring system

Scoring	Risk factors
0	WBC count>30x109
1	WBC count<4x109
2	Hb<10g/dl

International prognostic scoring system(dynamic)

scoring	IPSS At diagnosis	DIPSS At any time	DIPSS-Plus
Age >65years	+	+	+
Constitutional symptoms	+	+	+
Hb<10g/dl	+	+	+
WBC >25X109	+	+	+
Blood blast >1%	+	+	+
Platelets < 100x109/L			+
RBC transfusion need			+
Unfavorable karyotype +8,-7/7q-, -5/5q-, i17q, 12q-, 11q23 rearrangement			+
	1 point each	1 point each (Hb: 2 point)	High: 3points Intermediate 2: 2 points Intermediate 1: 1 points Platelets <100, unfavorable karyotyping, and transfusion need :1 point each
IPSS……Low risk=0 points, intermediate1 =1 point, intermediate2 risk=2 points, high risk=3-5 points. DIPSS…..low risk=0 point, intermediate risk1=1-2 points, intermediate2=3-4 points, high risk=5-6 points. DIPSS-plus…..low risk=0 point, intermediate risk1=1 points, intermediate2=2-3points, high risk=4-6 points.			

Treatment

Proposed approach to treatment of primary myelofibrosis:

	Age	Standard of care	Alternative options
Lille class 0	<45	Watchful waiting	SCT
	45-65	Watchful waiting	SCT
	>65	Watchful waiting	SCT/rIFN
Lille class I/II	<45	SCT	Small molecule therapy
	45-65	SCT	Small molecule therapy
	>65	Conventional ther-apy	Small molecule therapy /SCT up to age 70y

Therapy of Idiopathic Myelofibrosis:

Anemia

- B12, folic acid, iron deficiency anemia as possible contributing factors be identified and corrected.
- A trial of EPO (350u/kg/week)may be given to patients who are symptomatically anaemic and have serum EPO <125 U/l.
- Danazol 600mg per day should be maintain at least for 6 months, with tapering the dose to the minimum effective dose usually 200mg/day. Prostatic cancer screen must be carried out.
- α-interferon(recombinant) may increase the response rate of EPO
- Thalidomide 50mg/day or linalidomide 10mg/day alone or with combination with prednesolone 30mg/day may be efficacious in some cases.
- Chelation therapy in patients by desferoxamin or deferasirox who are serum ferritin more than 2500 ng%.

Splenomegaly and increase CBC indices:

- Hydroxyurea for: ↑platelets, ↑WBCs or hypermetabolic symptoms.
- Ruxolotinib 20mg x2 for the constitutional symptoms and splenomegaly after failure of hydroxyurea therapy. Adjust the dose according the platelets count and other blood indices.
- Splenectomy should only rarely be considered due to the high complication rate but indications may include symptomatic splenomegaly, hypersplenism, trauma or rupture, portal hypertension.
- Allopurinol prophylaxis
- Splenic irradiation for0.15-65GY per course: hypermetabolic symptoms, leucopenia, symptomatic splenomegaly or unfit for splenectomy and not respond to JAK2 inhibitors
- Purin analogue,2 CDA, decrease hepatomegally and thrombocytosis in post splenectomy MF patients.
- 5-azacitidine& decitabine may be used.

Constitutional symptoms

- Until the introduction of JAK inhibitors, the treatment of constitutional symptoms are unsatisfactory, although proportion of patients may obtain transient response to cytoreductive therapy and steroid.

Extramedullary hematopoiesis

- Low dose radiation therapy in place other than spleen
- JAK inhibitors/ off label

Polycythemia rubra vera

&

Essential thrombocythemia

Criteria of ET by BSCH 2010

requires A1-A3 or A1+ A3-5

A1- sustained platelet count >450x109/L .

A2- presence of an acquired pathogenic mutation(JAK2 or MPL)

A3- no other myeloid malignancy (PRV, PMF, CML, MDS)

A4- no reactive cause thrombocytosis and normal iron stores

A5- BM aspiration and biopsy showing increase megakaryocytic numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm.

or

Criteria of ET by WHO 2008

- requires A1-A4

A1- sustained platelet count >450x109/L .

A2- BM aspiration and biopsy showing increase numbers of enlarge, mature megakaryocytic numbers, no significant increase of left shift of granulopoisis or erythropoiesis

A3- no meeting WHO criteria for other myeloid malignancy (PRV, PMF, CML, MDS)

A4- acquired pathogenic mutation(JAK2 or MPL) or no reactive cause for thrombocytosis.

Criteria of PRV

- **Major criteria**

1- Hemoglobin level >18g/dl in men and > 16.5g/dl in women or evidence of increase red cell volume

2- presence of JAK2(V617F) or other functionally similar mutation (JAK exon 12 mutation)

- **Minor criteria**

1- BM biopsy specimen showing hypercellularity for age with trilineage myeloprolifertion

2- serum erythropoietin level below the normal reference range

3- endogenous erythroid colony formation in vitro

the diagnosis of PV requires meeting either both major criteria and 1 minor criteria or the 1st major criteria and 2 minor criteria.

Classification and risk stratification of essential thrombocythemia:

	Low risk	Intermediate risk	High risk
Age/years	<40	40-60	> 60
Previous history of thrombosis or hemor-rhage	negative	Negative	present
Hypertension, diabetes	Negative	Negative	Presence
Platelet count	<1.5x109	<1.5x109	>1.5X109

Treatment of ET
Choice of cytoreductive agent according the age:

Risk category	1st line	2nd line
<40years	• interferon	• Hydroxyurea • anagrelide
40-75years	• Hydroxyurea	interferon angrelide

>75years	• Hydroxyurea	• angrelide • busulphan • radioactive phosphorus

Treatment:

Risk category	Polycythaemia rubra vera	Essential thrombocythemia
Low	• Phlebotomies to reach for: Male <45% Female <42% • Low dose aspirin	• Nil • Possible benefit of aspirin
Intermediate	• Phlebotomies to reach for: Male <45% Female <42% • Low dose aspirin	Low dose of aspirin(no consensus)
High	• Myelosuppressive therapy: Hydroxyurea, alpha interferon±phlebotomies • Low dose aspirin	• Myelosuppressive therapy:Hydroxyurea, alpha Interferon • Low dose aspirin

◉For younger patients alpha interferon the preferred therapy.

◉For less side effect and easy uses peg. Interferon.

Resistant & intolerance of hydroxyurea criteria:

- Platelets >600x109after 3 months of at least 2g/day(2.5g/day for those patients Bwt. >80kg)
- Platelets >400x109&WBC<2.5X109 at any dose of hydroxyurea.
- Platelets >400x109&hb<10g/dl of hydroxyurea.
- Presence of leg ulcer or other unacceptable muco-cutaneous manifestations at any dose of hydroxyurea.
- Hydroxyurea related fever.

Chronic Myelomocytic Leukemia

Classical:

- Persistent peripheral blood (1 x 10^9/l) monocytosis (>3 months)
- <20% bone marrow blasts.
- Normal or MDS type cytogenetics.

Varient:

- CMML with eosinophilia and is rare but important, as this variant is sensitive to imatinib therapy.
- Refractory Anaemia with Ring Sideroblasts and thrombocytosis (RARS-t) is JAK2 mutated in 50% cases.
- A very rare variant is described without monocytosis but with increased neutrophil and immature myeloid cells in peripheral blood. This is termed atypical CML. Absence of *BCR-ABL* is essential and the report must describe this as an MDS variant to avoid confusion with CML

Treatment

CMML patients should be managed with supportive care for cytopenias and cytoreductive therapy with :

➢ hydroxycarbamide

➢ 5-azacitidine

➢ Glivec for CMML with eosenophilia

Hypereosinpophilic syndrome

Subtype of hypereosinophilic syndrome

- Myeloproliferative variant
- Lymphoproliferative variant

The myeloproliferative variant is often associated with a small interstitial deletion in chromosome 4 at the CHIC2 site that causes the FIP1L1/PDGFRA -associated fusion gene (which has tyrosine kinase activity that can transform hematopoietic cells). Patients often have

- Splenomegaly
- Thrombocytopenia
- Anemia
- Elevated serum vitamin B12levels
- Hypogranular or vacuolated eosinophils
- Myelofibrosis

Patients with this subtype often develop endomyocardial fibrosis and may rarely develop acute myeloid or lymphoblastic leukemia. Patients with the

FIP1L1/PDGFRA -associated fusion gene are more often males and may be responsive to low-dose imatinib.

The lymphoproliferative variant is associated with a clonal population of T cells with aberrant phenotype. PCR shows a clonal T cell receptor rearrangement. Patients more often have

- Angioedema, skin abnormalities, or both
- Hypergammaglobulinemia (especially IgE)
- Circulating immune complexes (sometimes with serum sickness)

They also more often respond favorably to corticosteroids and occasionally develop T-cell lymphoma.

Other HES variants include chronic eosinophilic leukemia, Gleich syndrome (cyclical eosinophilia and angioedema), familial hypereosinophilic syndrome mapped to 5q 31-33, and other organ-specific syndromes. Hyperleukocytosis may occur in patients with eosinophilic leukemia and very high eosinophil counts (eg, > 100,000 cells/μL). Eosinophils can form aggregates that occlude small blood vessels, causing tissue ischemia and microinfarctions. Common manifestations include brain or lung hypoxia (eg, encephalopathy, dyspnea or respiratory failure).

Diagnosis

- Evaluation for HES should be considered in patients who have peripheral blood eosinophilia >1500/μL present on more than one occasion that is unexplained, particularly when there are manifestations of organ damage.
- Testing to exclude disorders causing eosinophilia should be done.

- Further evaluation for organ damage should include blood chemistries (including liver enzymes, creatine kinase, renal function, and troponin); ECG; echocardiography; pulmonary function tests; and CT of the chest, abdomen, and pelvis.
- Bone marrow aspirate and biopsy with flow cytometry, cytogenetic testing, and reverse transcriptase-PCR or fluorescence in situ hybridization (FISH) is done to identify the FIP1L1/PDGFRA -associated fusion gene and other possible causes of eosinophilia (eg, BCR-ABL abnormalities characteristic of chronic myelogenous leukemia).

Treatment

Treatments include immediate therapy, definitive therapies (treatments directed at the disorder itself), and supportive therapies.

- Corticosteroids for hypereosinophilia and often for ongoing treatment of organ damage
- Imatinib for patients with the *FIP1L1/PDGFRA* -associated fusion gene
- Sometimes drugs to control eosinophil counts (eg, hydroxyurea, interferon alfa, etoposide, cladribine)
- Supportive therapy

Immediate therapy

For patients with very severe eosinophilia, complications of hyperleukocytosis, or both (usually patients with eosinophilic leukemia), high-dose IV corticosteroids (eg, prednisone 1 mg/kg or equivalent) should be initiated as soon as possible. If the eosinophil count is much lower (eg, by ≥ 50%) after 24 h, corticosteroid dose can be repeated daily; if not, an alternative treatment (eg, hydroxyurea) is begun. Once the eosinophil count begins to decline and is under better control, additional drugs may be started.

Definitive therapy

Patients with the *FIP1L1/PDGFRA* -associated fusion gene are usually treated with imatinib and, particularly if heart damage is suspected, corticosteroids. If imatinib is ineffective or poorly tolerated, another tyrosine kinase inhibitor (eg, dasatinib, nilotinib, sorafenib) can be used, or allogenic hematopoietic stem cell transplantation can be used.

Patients without the *FIP1L1/PDGFRA* -associated fusion gene, even if asymptomatic, are often given one dose of prednisone 60 mg (or 1 mg/kg) po to determine corticosteroid responsiveness (ie, a decrease in the eosinophil count). In patients with symptoms or organ damage, prednisone is continued at the same dose for 2 wk, then tapered. Patients without symptoms and organ damage are monitored for at least 6 mo for these complications.

If corticosteroids cannot be easily tapered, a corticosteroid-sparing drug (eg, hydroxyurea, interferon alfa) can be used.

Supportive therapy

Supportive drug therapy and surgery may be required for cardiac manifestations (eg, infiltrative cardiomyopathy, valvular lesions, heart failure). Thrombotic complications may require the use of antiplatelet drugs (eg, aspirin, clopidogrel, ticlopidine); anticoagulation is indicated if a left ventricular mural thrombus is present or if transient ischemic attacks persist despite use of aspirin.