GROUPE
QUÉBÉCOIS
DE RECHERCHE EN
LMC-NMP

MYELOPROLIFERATIVE NEOPLASMS TREATMENT GUIDELINES

Version 2018

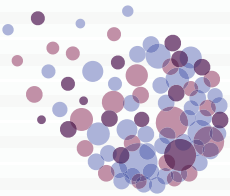
The Groupe québécois de recherche en leucémie myéloïde chronique (LMC) et néoplasies myéloprolifératives (NMP) is a nonprofit organization founded in 2011. It consists of hematologists with an expertise in chronic myeloid leukemia (CML) and myeloproliferative neoplasms (MPN) which come from a majority of health care institutions in the Province of Quebec.

The mission of the *Groupe québécois de recherche en LMC-NMP* (GQR LMC-NMP) is to:

- Facilitate innovative clinical research in CML and MPN,
- Optimize clinical management of CML and MPN,
- Assure a rapid and efficient transition of research to clinical practice,
- Offer continuing professional development relative to CML and MPN.

MPN TREATMENT **GUIDELINES**

VERSION 2018



GROUPE
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LMC-NMP

ESSENTIAL THROMBOCYTOSIS (ET)

INITIAL INVESTIGATION

- **Propose enrolment in the MPN Registry of the GQR LMC-NMP.**
- **Medical history:**
  - MPN symptoms (complete the MPN-SAF TSS if possible):
    - **Cytokines:** Fever, night sweats, fatigue, weight loss,
    - **Hyperviscosity:** Erythromelalgia, headache, visual disturbances, ringing in ears, impaired concentration,
    - **Splenomegaly:** abdominal fullness or discomfort, early satiety;
  - Venous thromboembolic history (DVT, PE) and/or vascular disease (neurologic, cardiologic or peripheral);
  - Risk factors for cardiovascular disease: Arterial hypertension, diabetes, dyslipidemia, and tobacco use;
  - Familial history of hematological neoplasia, particularly myeloproliferative (within two generations).
- **Physical examination:**
  - Document spleen size (in cm below the costal margin);
  - Consider abdominal imaging (ultrasound preferred) if the physical exam is unreliable to document the spleen size.
- **Blood analysis:**
  - CBC (with differential and smear), electrolytes, creatinine, LDH, uric acid, bilirubin, AST, ALT, Alk P., GGT, ferritin, C-reactive protein, fasting glucose, cholesterol (total, LDL, HDL), HbA1c;
  - Screening coagulogram;
  - In patients with a platelet count > 1 000 x 10^9/L testing for acquired von Willebrand disease is recommended

- Molecular diagnosis:
  - *JAK2 V617F* mutation testing; a quantitative assay may be advantageous for diagnosis and prognostication especially if disease modifying therapy is being considered.
  - If *JAK2 V617F* absent, proceed with *CALR* mutation testing.
  - If both are absent, proceed with *MPL S505* or *MPL W515* testing on blood or bone marrow.
  - In the absence of *JAK2, CALR or MPL mutations*, exclude CML (*BCR-ABL1* testing) if not done initially.

- **Bone marrow aspiration and biopsy:**
  - Should ideally be performed in all patients to confirm the diagnosis (WHO criteria) and or before initiating a cytoreductive treatment to distinguish true ET and pre-fibrotic myelofibrosis (MF);
  - Essential in the absence of a *JAK2* or *CALR* mutation;
  - Karyotype on bone marrow aspirate:
    - Undertake this analysis if a doubt persists on the diagnosis.

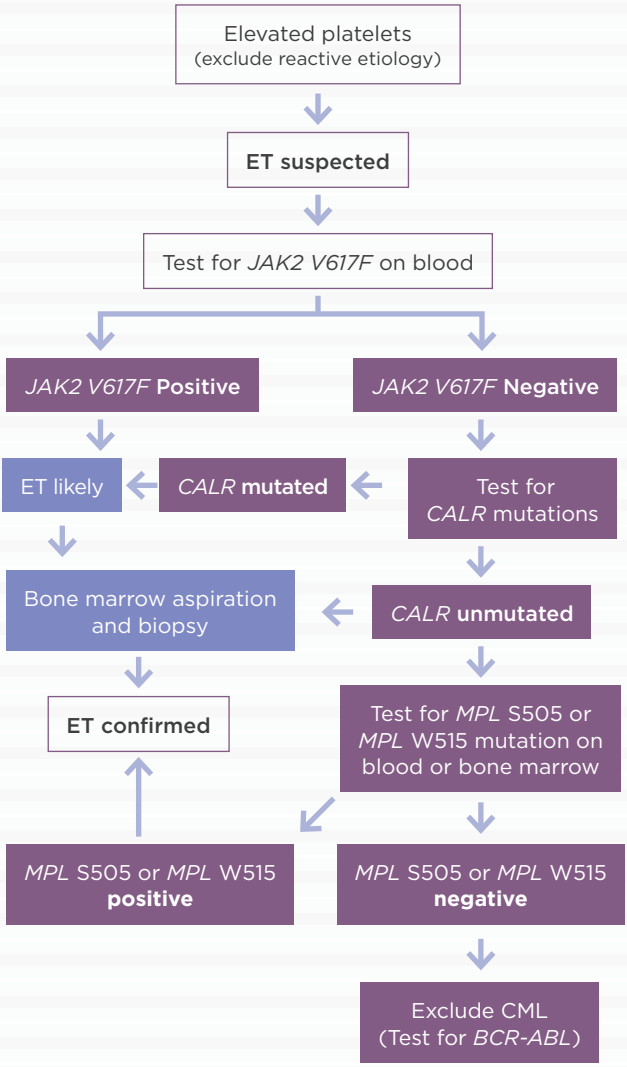
- **Fertility and pregnancy:**
  - In younger patients, discuss the potential effect of the disease and treatments on fertility and pregnancy.

DETERMINATION OF RISK CATEGORY:

- **IPSET – thrombosis:**
  - 1 point scored for:
    - Age ≥ 60
    - Presence of cardiovascular risk factors
  - 2 points scored for:
    - History of thrombosis
    - Presence of the *JAK2 V617F* mutation
  - Point based risk:
    - Low risk: 0-1 point
    - Intermediate risk: 2 points
    - High risk: >2 points

MPN: Myeloproliferative neoplasms; DVT: Deep vein thrombosis; PE: Pulmonary embolism; CBC: complete blood count; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Alk P.: alkaline phosphatase; GGT: gamma glutamyltransferase; LDL: low density lipoprotein; HDL: high density lipoprotein; HbA1c: glycated hemoglobin; EPO: erythropoietin; b12

Figure 1. Proposed algorithm for ET diagnosis



TREATMENT:

- **Antiplatelet therapy:**
  - All high risk ET patients without contraindication and absence of acquired von Willebrand should be initiated on antiplatelet therapy (acetylsalicylic acid 80 mg once daily);
  - In low risk patients the benefit is less clear, however we recommend acetylsalicylic acid in low risk patients who do not have a clear contraindication, particularly *JAK2* mutated patients.
- **Cytoreductive Therapy:**
  - Cytoreductive therapy is recommended in patients who are at high risk of thrombotic complications;
  - It can be considered in patients at low risk if they have any of the following conditions:

    a) Platelet count ≥ $1500x10^9$/L*

    b) Progressive leukocytosis ≥ $25x10^9$/L

    c) Symptomatic splenomegaly

    d) Severe disease-related symptoms (such as erythromelalgia refractory to acetylsalicylic acid)

  * Platelet count ≥ $1500x10^9$/L is also associated with a bleeding risk.

- **Clinical trial:**
  - Consider if available. A list of active clinical trial in Quebec is available at **gqr-lmc-nmp.ca**
- **Therapeutic target:**
  - Platelets count < upper limit of normal (ULN);
  - Absence of thrombosis;
  - Absence of bleeding.

CHOICE OF CYTOREDUCTIVE AGENT:

First line:

- **Hydroxyurea:**
  - Is considered as first line agent in all patients.
    - Starting dose is 500 mg daily titrated every 2-4 weeks to a platelet count below ULN.
- **Interferon:**
  - Both short acting interferon-α or pegylated interferon can be considered as first line agents especially in younger patients (< 40 years) where fertility issues may arise:
    - Starting dose for pegylated interferon is 45 to 90 μg subcutaneously every week;
    - Starting dose of interferon-α is 1 million units subcutaneously 3x/ week;
    - Titrate monthly monitoring tolerance and blood counts.
  - Prior to initiation of interferon, screening for psychiatric illness, autoimmune disease, thyroid disorders and liver dysfunction should be undertaken.

DEFINITIONS OF FIRST LINE FAILURE OR INTOLERANCE DEFINITIONS*

1. **Platelets count > ULN after 3 months of hydroxyurea treatment at 2g daily, OR**
2. **Platelets count > ULN AND neutrophils** < normal at any dose of hydroxyurea, OR**
3. **Platelets count > ULN and Hb < 100g/L at any dose of hydroxyurea, OR**
4. **Presence of leg ulcers or other non-haematological toxicity related to the cytoreductive agent, such as cutaneous or mucosal lesions, gastrointestinal symptoms, pneumonitis or fever, at any dose.**

* Adapted from European LeukemiaNet (ELN)

** Treatment may be continued despite a value below normal if it is considered clinically appropriate by the treating physician

Second line therapies:

- **Anagrelide:**
  - Can be used in patient who are intolerant to hydroxyurea:
    - Starting dose of 0,5 mg po bid titrated 2-4 weekly to a platelet count below ULN;
    - Caution in elderly patients and patients with heart disease as anagrelide has been associated with cardiac dysfunction, arrhythmias and heart failure.
- **Busulfan:**
  - Has a limited role because of its leukemogenic potential; considered only in elderly patients (age > 80):
    - Recommended starting dose is 2-4 mg daily until therapeutic target is reached;
    - Many patients maintain a hematologic response despite discontinuing busulfan, and may only require a 2-3 week course every 4-6 months.
- **Interferon:**
  - Both short acting interferon-α or pegylated interferon can be considered as a second line agents especially in younger patients (< 40 years) where fertility issues may arise:
    - Starting dose for pegylated interferon is 45 to 90 ug subcutaneously every week;
    - Starting dose of interferon-α is 1 million units subcutaneously 3x/ week;
    - Titrate monthly monitoring tolerance and blood counts.
  - Prior to initiation of interferon, screening for psychiatric illness, autoimmune disease, thyroid disorders and liver dysfunction should be undertaken.

MONITORING/FOLLOW-UP:

- Close follow-up until the therapeutic target is reached and following dose or treatment modification.
- If stable, follow-up every 3-4 months with:
  - Physical examination including documentation of the spleen size,
  - CBC, creatinine, LDH, bilirubin, AST, ALT.
- Follow-up and assessment of cardiovascular disease risk factors, if not done by another physician caring for the patient.

PROGRESSION TO MYELOFIBROSIS OR ACUTE LEUKEMIA

- **Progression should be suspected with:**
  - Appearance of a leukoerythroblastic peripheral blood smear,
  - Progressive leukocytosis with left shift,
  - Cytopenia despite decrease in cytoreductive agents,
  - Progressive splenomegaly,
  - Unexplained rise in LDH,
  - Appearance of constitutional symptoms.
- **The diagnosis requires a bone marrow biopsy with:**
  - Reticulin and collagen staining,
  - Cytogenetic study.
- **Treatment of progression to myelofibrosis should follow the same principles as primary myelofibrosis**

POLYCYTHEMIA VERA (PV)

INITIAL INVESTIGATION

- **Propose enrolment in the MPN Registry of the GQR LMC-NMP.**
- **Medical history:**
  - MPN symptoms (consider filling out MPN-SAF TSS):
    - **Cytokines:** Fever, night sweats, aquagenic pruritis, fatigue, weight loss,
    - **Hyperviscosity:** Erythromelalgia, headache, visual disturbances, ringing in ears, impaired concentration problems,
    - **Splenomegaly:** abdominal fullness or discomfort, early satiety;
  - History of venous thromboembolic episodes (DVT, PE) and for vascular disease (neurologic, cardiologic or peripheral);
  - Risk factors for cardiovascular disease: Arterial hypertension, diabetes, dyslipidemia, and tobacco use;
  - Familial history of hematological neoplasia, particularly myeloproliferative (within two generations).
- **Physical examination:**
  - Document spleen size (in cm below the costal margin).
- **Blood analysis:**
  - CBC (with differential and smear), electrolytes, creatinine, LDH, uric acid, bilirubin, AST, ALT, Alk. P., GGT, fasting glucose, cholesterol (total, LDL, HDL), HbA1c;
  - EPO level;
  - *JAK2 V617F* mutation testing; a quantitative assay may be advantageous for diagnosis and prognostication especially if disease modifying therapy is being considered.

INITIAL INVESTIGATION (CONTINUED)

- **Imaging:**
  - Consider abdominal ultrasound for unreliable physical exam or history suggestive of secondary polycythemia. An abdominal and pelvic CT scan is more sensitive in identifying secondary causes;
  - Imaging must be undertaken if EPO level is normal/high and/or *JAK2* mutation is absent.
- **Fertility and pregnancy:**
  - In younger patients, discuss the potential effect of the disease and treatments on fertility and pregnancy.

INTERPRETATION OF PRIMARY INVESTIGATIONS

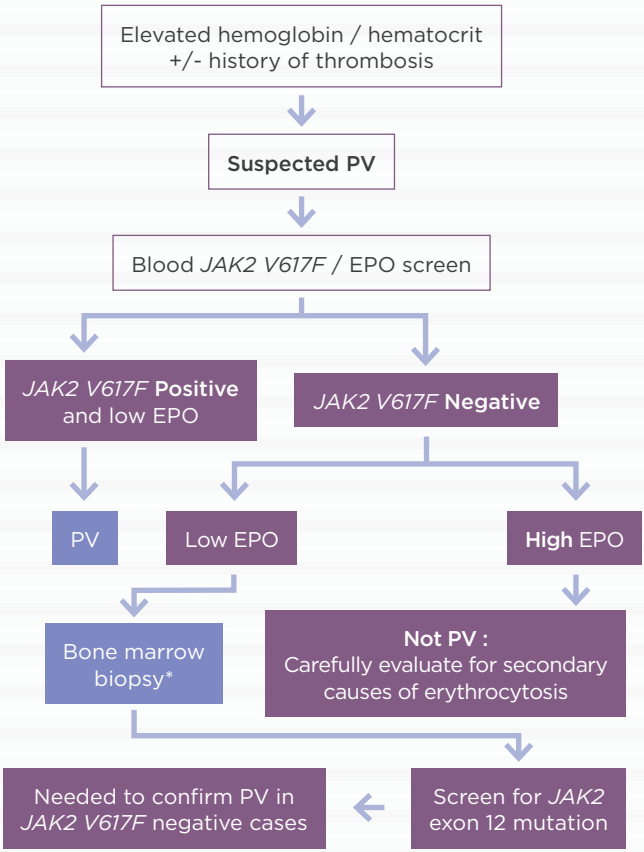
- **If *JAK2 V617F* is present and EPO level subnormal:**
  - The diagnosis of PV is confirmed.
- **If *JAK2 V617F* is absent and EPO level subnormal:**
  - This may be PV:
    - > Requires a bone marrow aspirate and biopsy with *JAK2* exon 12 mutation analysis (see the following section on bone marrow aspirate and biopsy);
    - > If exon 12 normal, consider familial etiology.
- **If *JAK2 V617F* is absent and EPO is normal or high:**
  - This is unlikely to be PV. Investigate secondary causes of erythrocytosis.

COMPLEMENTARY INVESTIGATIONS

- **Bone marrow aspiration and biopsy**
  - In *JAK2 V617F* mutated patients with erythrocytosis, WHO 2016 recommends a bone marrow examination to confirm the diagnosis. This test may provide prognostic value, however we recognize that in routine clinical practice this analysis is not always necessary;
  - This analysis is essential in suspected PV cases where *JAK2 V617F* is absent;
  - Sometimes the biopsy undertaken in the investigation of another MPN may provide evidence of PV or masked PV by demonstrating increased trilineage myelopoeisis.
- **Analysis for a *JAK2* exon 12 mutation**
  - Must be undertaken on a bone marrow aspirate in the absence of a peripheral blood *JAK2 V617F* mutation and EPO values below normal.

- **Stem cell culture**
  - A culture for endogenous colonies can be undertaken, if available, with all bone marrow aspirates.
- **Marrow karyotype**
  - In an unequivocal PV, it is not recommended to perform routine bone marrow karyotyping.
    - However, if another MPN is suspected (particularly myelofibrosis) this analysis should be included with the aspirate.

Figure 2. Proposed algorithm for PV diagnosis



* A diagnosis of PV can be made without bone marrow biopsy in a patient with hemoglobin > 185 g/L (55.5% hematocrit (HT) in men or > 165 g/L (49.5% HT) in women and in the presence of the *JAK2 V617F* mutation (WHO 2016).

DETERMINATION OF RISK CATEGORY:

- **High risk:**
  - Age ≥ 60 and/or history of venous or arterial thrombotic events.
- **Low risk:**
  - Age < 60 and absence of thrombotic history.

TREATMENT

- **Antiplatelet therapy:**
  - All patients without a clear contraindication to acetylsalicylic acid should be started on a daily dose of 80 mg.
- **Phlebotomy:**
  - Phlebotomy must be initiated in all patients and continued to maintain a hematocrit of < 45%;
  - Phlebotomy can be performed by removing up to 400-500 ml of blood weekly until the therapeutic target is reached;
  - Smaller volumes or isovolumetric replacement with normal saline may be considered in elderly patients;
  - More aggressive phlebotomy regimes (e.g. twice weekly) can be considered in the symptomatic patient who tolerates initial phlebotomy.
- **Cytoreduction:**
  - Cytoreductive therapy is recommended in patient who are at high risk of thrombotic complications (age ≥ 60 and/or history of thrombosis).
  - It can be considered in patients at low risk if they have any of the following:
    a) Platelet count ≥ $1500x10^9$/L*,
    b) Progressive leukocytosis ≥ $25x10^9$/L,
    c) Symptomatic splenomegaly,
    d) Severe disease-related symptoms (such as erythromelalgia refractory to aspirin/hematocrit reduction or pruritus),
    e) Intolerance to phlebotomy especially in patients with compromised cardiac function, inability to comply with phlebotomy requirements or poor venous access.

* Platelet count ≥ $1500x10^9$/L is also associated with a bleeding risk.

- **Clinical trial:**
  - Consider if available. A list of active clinical trials in Quebec is available at **gqr-lmc-nmp.ca**
- **Therapeutic target for cytoreduction:**
  - Hematocrit of < 45% after 3 months without phlebotomy;
  - Absence of thrombosis.

CHOICE OF CYTOREDUCTIVE AGENT:

First line:

- **Hydroxyurea:**
  - First line agent in all patients. The starting dose is 500 mg daily to be titrated every 2-4 weeks until the target hematocrit (<45%) is reached.
- **Interferon:**
  - Both short acting interferon-α or pegylated interferon can be considered as a first line cytoreductive agents especially in younger patients (< 40 years of age) where fertility issues may arise:
    - The starting dose for pegylated interferon is 45 to 90 μg subcutaneously every week;
    - Starting dose of interferon-α is 1 million units subcutaneously 3x/ week;
    - Titrate monthly monitoring tolerance and blood counts.
  - Prior to initiation of interferon, screening for psychiatric illness, autoimmune disease, thyroid disorders and liver dysfunction should be undertaken.

DEFINITIONS OF FIRST LINE FAILURE OR INTOLERANCE DEFINITIONS *

1. **Need of phlebotomy to maintain the HT < 45%**.**
2. **Uncontrolled myeloproliferation** ^.**
3. **Failure to reduce massive splenomegaly (> 10 cm below the costal margin) of at least 50% as measured by palpation, OR failure to completely relieve the symptoms caused by splenomegaly.**
4. **Absolute neutrophil count <1.0x10^9/L or platelets <100x10^9/L or hemoglobin <100 g/L at the lowest cytoreductive agent dose required to achieve the therapeutic target.**
5. **Presence of leg ulcers or other non-haematological toxicity related to the cytoreductive agent, such as cutaneous or mucosal lesions, gastrointestinal symptoms, pneumonitis or fever, at any dose.**
6. **Thrombosis**

* Adapted from European LeukemiaNet (ELN)
** After 3 months to at least 2g/day of HU
^ A leukocyte level > 15.0x10^9/L is associated with a poor prognosis and decreased survival, while a platelet level ≥ 1500x10^9/L is also associated with a risk of bleeding

Second line therapies:

- **Ruxolitinib:**
  - Approved by Health Canada for patients with PV who are resistant or intolerant to a cytoreductive agent:
    - The starting dose is 10 mg twice daily
    - Consider zoster vaccines prior to initiation of therapy
    - **Abrupt drug interruption may lead to a shock-like syndrome due to cytokine release. This drug should be tapered rather than interrupted abruptly.**

- **Busulfan:**
  - Has a limited role, only in very elderly patients (age > 80) because of its leukemogenic potential:
    - The recommended starting dose is 2-4 mg daily until target Hct is reached
    - Many patients maintain a hematologic response despite discontinuing busulfan, and may only require a 2-3 week course every 4-6 months.
- **Interferon:**
  - Both short acting interferon-α or pegylated interferon can be considered in second line
    - The starting dose for pegylated interferon is 45 to90 μg subcutaneously every week;
    - With interferon-α, the starting dose is 1 million units subcutaneously 3x/ week;
    - To be adjusted monthly monitoring to the tolerance and the blood count.
  - Prior to initiation of interferon, screening for psychiatric illness, autoimmune disease, thyroid disorders and liver dysfunction must be undertaken.

OTHER THERAPY

- **Symptomatic Pruritis:**
  - Antihistamines as first line agents (eg hydroxyzine 10-25 mg po q4-6h prn) or
  - SSRI (eg. paroxetine 10-20 mg once daily) as a second line agent.

MONITORING/FOLLOW-UP:

- Same as ET. See page 7

PROGRESSION TO MYELOFIBROSIS OR ACUTE LEUKEMIA

- Same as ET. See page 7
- Loss of phlebotomy requirements

MYELOFIBROSIS (MF)

INITIAL
INVESTIGATION

Propose enrolment in the MPN Registry of the GQR LMC-NMP.

- **Medical history:**
  - MPN symptoms (consider filling out MPN-SAF TSS):
    - **Cytokines:** Fever, night sweats, aquagenic pruritis, fatigue, weight loss;
    - **Hyperviscosity:** Erythromelalgia, headache, visual disturbances, ringing in ears, impaired concentration;
    - **Splenomegaly:** abdominal fullness or discomfort, early satiety;
  - History of venous thromboembolic episodes (DVT, PE) and of vascular disease (neurologic, cardiologic or peripheral);
  - Risk factors for cardiovascular disease: Arterial hypertension, diabetes, dyslipidemia, and tobacco use;
  - Familial history of hematological neoplasia, particularly myeloproliferative (within two generations).
- **Physical examination:**
  - Must document spleen size (in cm below the costal margin);
  - Examine for hepatomegaly;
  - Obtain abdominal imaging (ultrasound preferred) for documenting the size of the spleen & liver (imaging required for the reimbursement of certain treatments).

- **Blood analysis:**
  - CBC (with differential and smear), electrolytes, creatinine, LDH, uric acid, bilirubin, AST, ALT, Alk P., GGT, fasting glucose, cholesterol (total, LDL, HDL), HbA1c;
  - EPO level if the patient is anemic;
  - *JAK2 V617F* mutation testing. A quantitative assay may be advantageous for diagnosis and prognostication especially if disease modifying therapy is being considered.
    - > If *JAK2 V617F* is negative proceed with *CALR* mutation testing.
    - > If *CALR* is unmutated proceed with *MPL* mutation testing.
- **Bone marrow aspiration and biopsy:**
  - A bone marrow biopsy is a WHO criteria for the diagnosis of MF.
- **Marrow karyotype:**
  - Cytogenetic analysis must be performed in all patients with suspected MF (Provides prognostic value in DIPSS plus score);
  - We recognize that the MF patients' bone marrow may be difficult to aspirate. A core biopsy or peripheral blood sample for karyotype may be obtained.
    - > Favorable karyotypes: normal, sole 13q-, sole 20q-, sole +9, single chromosome 1 translocation/duplication, single other abnormalities, and two abnormalities without an unfavorable type.
    - > Unfavorable karyotype: complex karyotype or abnormalities including +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3) or 11q23 rearrangement.
- **Complementary investigations:**
  - In the absence of *JAK2*, *CALR*, and *MPL* mutations, rule out CML (*BCR-ABL1* testing) if not done initially;
  - Screening for genetic mutations, (next generation sequencing, genetic panels or targeted genes) has been reported to refine prognostic scoring systems but remains exploratory for funding agencies and is not a routine investigation at the present time.
- **Fertility and pregnancy:**
  - In younger patients, discuss the potential effect of the disease and treatments on fertility and pregnancy.

DETERMINATION OF PROGNOSTIC RISK CATEGORY:

- **At Diagnosis the IPSS can be used**
- **The DIPSS and DIPSS Plus can be used at anytime during the course of the disease**

Variable	IPSS (IWG-MRT)	DIPSS	DIPSS Plus (Mayo Clinic)
Age ≥ 65 ans	1 point	1 point	1 point for DIPSS INT-I 2 points for DIPSS INT-II 3 points for DIPSS High
Constitutional symptoms	1 point	1 point	
Hb: < 100 g/L	1 point	2 points	
Leukocytes > 25x10⁹/L	1 point	1 point	
Circulating blasts ≥ 1%	1 point	1 point	
Platelets < 100 x 10⁹/L			1 point
RBC transfusion need			1 point
Unfavorable karyotype*			1 point
Low risk	0 point	0 point	0 point
Intermediate-I	1 point	1-2 points	1 point
Intermediate-II	2 points	3-4 points	2-3 points
High risk	3-5 points	5-6 points	4-6 points

* An unfavourable karyotype would be defined as a complex karyotype or abnormalities including +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3) or 11q23 rearrangement. .

MANAGEMENT:

1. Determine prognostic risk category
2. Determine extent of symptomatology
3. Establish potential transplant eligibility

- **Management of anemia:**
  - See the special situations section on page 20
- **Antiplatelet therapy:**
  - There is no clear recommendation on the use of acetylsalicylic acid but it would be reasonable to consider it in the absence of a contraindication in the following situations:
    - Platelets > 50 x 10^9/L AND
    - Patients ≥ 60 years old, or
    - Thrombotic history, or
    - Cardiovascular risk factor, or
    - *JAK2 V617F* present.
- **Therapeutic target:**
  - Treat constitutional symptoms and symptomatic splenomegaly.

LOW /INT I RISK PATIENTS:

If asymptomatic:

- These patients do not require MF directed therapy. They should be assessed clinically every 3-4 months.
- At each visit, a physical exam with documentation of spleen size should be performed, a CBC, blood smear and LDH level.

If constitutional symptoms:

First line:

- A trial of cytoreduction with hydroxyurea at a starting dose of 500 mg/day is reasonable.

Second line:

- Consider clinical trials if available. A list of active clinical trials in Quebec is available at **gqr-lmc-nmp.ca**
- A *JAK* inhibitor should be considered if available. Although these agents are not always reimbursed for patients with low risk disease, they can improve constitutional symptoms.

LOW /INT I
RISK PATIENTS (CONTINUED):

Symptomatic treatment of pruritus:

- 1st line: Antihistamines (e.g. hydroxyzine 10-25 mg po q4-6h).
- 2nd line: SSRIs (e.g. paroxetine 10-20 mg daily).

- If symptomatic due to cytopenias please see section on special situations below.
- In severely affected and refractory patients, an evaluation at a transplant centre should be considered.

INT II/ HIGH
RISK PATIENTS:

- **Transplant eligible patients:**
  - Refer to a center with expertise in evaluation of this therapeutic option.
    - HLA type patients` siblings and search for an alternate donor if possible
    - Treat symptoms while awaiting transplant.
- **Transplant ineligible patients:**
  - Determine symptomatology with the aid of the MPN SAF-TSS questionnaire.

If asymptomatic

- No treatment is necessary,
- Follow up clinically every 2 months.

In the presence of constitutional symptoms / symptomatic splenomegaly:

First line:

- Consider clinical trials if available. The list of active clinical trials is available at **gqr-lmc-nmp.ca**
- Ruxolitinib 5 to 20 mg twice daily (maximum dose 20 mg twice daily). Increase the dose every 4 weeks to reach the maximum tolerated dose within 4 to 6 months.
  - Consider zoster vaccines prior to initiation of therapy
  - **Abrupt drug interruption may lead to a shock-like syndrome due to cytokine release. This drug should be tapered rather than interrupted abruptly.**

Second line treatment:

- There are no approved second line treatments after failure of ruxolitinib.
- Consider clinical trials if available. A list of active clinical trials in Quebec is available at **gqr-lmc-nmp.ca**.
- Patients should be treated symptomatically.

Initial dose (mg po bid)	Recommendations
20	Hb > 120 g/L and platelets > 150 x 10^9/L
15	Hb between 100-120 g/L or platelets 100-150 x 10^9/L
10	Hb ≤ 100 g/L or platelets between 50-100 x 10^9/L
10	Platelets < 100 x 10^9/L
5	Platelets < 50 x 10^9/L

SPECIAL SITUATIONS

- **Management of anemia:**
  - A trial of epoetine alpha is recommended
    - Starting dose 40,000 units s.c weekly
    - Dose escalation every 3-4 weeks for a total duration of 8-12 weeks (increase to 60,000 U and if not effective divide in 2-3 weekly doses)
    - Patients with a high level of EPO (> 200 U / L) may have a suboptimal response.
  - If no response:
    - Danazol 100-300 mg twice daily may be considered. Titrate over several months from lowest daily dose following liver function and hematologic response.
    - If no response to danazol after 6 months, immunomodulators may be considered:
      - Low dose thalidomide (50 mg once daily) combined with oral prednisone (0.5 mg/kg) can be tried.
      - Lenalidomide (5-10 mg once daily) can be tried with del(5q) patients.
      - Single agent prednisone at a dose of 30mg once daily for 4 weeks followed by 15 mg once daily, can be used in patients with refractory anemia who do not respond to the aforementioned drugs.

SPECIAL SITUATIONS (CONTINUED)

- Transfusion support for symptomatic anemia should be provided. Iron chelation therapy according to standard practice may be considered as needed for patients with an anticipated survival of more than 12 months.

- **Management of thrombocytopenia:**
  - Avoid antiplatelet agents in patients with platelet counts < 50 x 10^9/L.
  - Platelet transfusions should only be administered in patients with active bleeding or prior to invasive procedures.
  - Antifibrolytics can be considered in individual cases with active bleeding but must be weighed against the prothrombotic risk of MPN.
  - There are no data on the use of active thrombopoietin receptor agonists in MPN.

- **Management of neutropenia:**
  - Patients with asymptomatic neutropenia do not need prophylactic treatment.
  - Neutropenic patients who develop infections can be treated with filgrastim at the minimally effective dose.

- **Management of asymptomatic patients without splenomegaly but with myeloproliferative features such leukocytosis and thrombocytosis:**
  - These patients can achieve hematologic control with hydroxyurea.

- **Management of cytopenias on ruxolitinib:**

  Starting at a lower dose of ruxolitinib and titrating up will serve to reduce the incidence and severity of cytopenias.

  Anemia:
  - A drop from the baseline Hb is expected at the beginning of treatment and reaches a nadir at about 8-12 weeks.
  - During the initial 8-12 weeks symptomatic anemia can be managed with
    - Transfusion support
    - A trial of epoetine alpha at a starting dose of 40,0000 units s.c weekly (as described above) despite the inhibition of *JAK2* signalling from the EPO receptor

Thrombocytopenia:

- Mild thrombocytopenia does not require dose adjustment.
- If the platelet count drops below 50 x 10^9/L, the ruxolitinib dose should be reduced by 5 mg po bid increments. A single daily dose is not recommended.
- For platelet counts below 30 x 10^9/L, ruxolitnib should be used with caution weighing the risks and benefits.

Neutropenia:

- Severe neutropenia due to ruxolitinib is rare. Disease progression should be excluded.
- If the neutrophil count drops below 500 x 10^9/L, the ruxolitinib dose should be reduced by 5 mg po bid increments. A single daily dose is not recommended.
- If dose reduction does not lead to improvement then a trial of filgrastim at a minimally effective dose (e.g.300 ug sc 3x/week) is warranted in patients who develop infections complications.

CRITERIA FOR LEUKEMIC TRANSFORMATION

- **Accelerated phase**
  - From 10 to 19% of blasts in peripheral blood or bone marrow in two different assays within 4 weeks.
- **Blast phase:**
  - More than 20% of blasts in peripheral blood or bone marrow in two different assays within 4 weeks.

ANNEX 1

ET DIAGNOSTIC CRITERIA
WHO 2016

Major criteria:

- 1. Platelet count >450 x 10^9/L
- 2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
- 3. Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasms
- 4. Presence of *JAK2, CALR* or *MPL* mutation

Minor criteria:

- 1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Diagnosis requires meeting all four major criteria or the first three major criteria and the minor criterion.

PV DIAGNOSTIC CRITERIA
WHO 2016

Major criteria:

- 1. Hemoglobin >16.5 g/dL (>165 g/L) in men
  Hemoglobin >16.0 g/dL (>160 g/L) in women

  or

  Hematocrit >0.49 in men
  Hematocrit >0.48 in women

  or

  Increased RBC mass*

- 2. Bone marrow biopsy specimen showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
- 3. Presence of *JAK2 V617F* or *JAK2* exon 12 mutation

Minor criteria:

- 1. Subnormal serum erythropoietin level

Diagnosis requires meeting either all three major criteria or the first two major criteria and the minor criterion.

* More than 25% above mean normal predicted value.

Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels more than 18.5 g/dL in men (hematocrit 55.5%) or more than 16.5 g/dL in women (hematocrit 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV myelofibrosis).

MF DIAGNOSTIC CRITERIA
WHO 2016

Major criteria:

- 1. Presence of megakaryocyte proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grade 2 or 3
- 2. Not meeting WHO criteria for ET, PV, CML, MDS, or other myeloid neoplasms
- 3. Presence of *JAK2*, CALR, or MPL mutation or, in the absence of these mutations, presence of another clonal marker[a] or absence of reactive myelofibrosis[b]

Minor criteria:

- 1. Anemia not attributed to a comorbid condition
- 2. Leukocytosis 11 x 10^9/L
- 3. Palpable splenomegaly
- 4. LDH increased to above upper normal limit of institutional reference range
- 5. Leukoerythroblastosis

Diagnosis requires meeting all three major criteria and at least one minor criterion.

[a] In the absence of any of the three major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) is of help in determining the clonal nature of the disease.

[b] Fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

The current guidelines are intended as a reference framework to present management strategies for myeloproliferative neoplasms. These guidelines are a consensus of the *Groupe québécois de recherche en LMC-NMP* based on published data as well as expert opinion and developed during consensus meetings. They do not replace in any way clinical judgment and are not intended to establish a treatment protocol that would be applicable to all cases of MPN.

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