Nordic guidelines on the diagnosis and treatment of patients with Myeloproliferative Neoplasms

The Nordic study group on myeloproliferative neoplasms (NMPN) is a pan-Nordic organization that has conducted Nordic clinical trials since 2001. NMPN decided in 2006 to write new guidelines, based on already existing national guidelines from the Nordic countries, Italy[1] and Great Britain.[2] The first version was published in 2007. The aim has been to write a document that can be used in all Nordic countries. We have strived to use evidence-based medicine, i.e. the conscientious, explicit, and judicious use of current best evidence in making decisions on our recommendations. The grading system employed in these guidelines is detailed on page 31. However, it should be stressed that few randomized controlled trials exist in the MPNs to support decision-making for individual patients. The guidelines are written for health professionals with a specialty or interest in hematology. They have now been updated in 2013, and are for the most part similar to those recently published by the European Leukemia Net.[3] This is the third update since our guidelines were first published.

For the Nordic MPN Group, January 2013

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General introduction

The Philadelphia chromosome/bcr-abl negative myeloproliferative neoplasms (MPNs) represent a range of clonal hematological diseases with overlapping features. The main entities are polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) which are characterized by clonal excess hematopoiesis in one or more cell lines. They are associated with an elevated risk of arterial and venous thrombosis; many PV and ET patients have thrombosis at the time of diagnosis. Both PV and ET can progress to myelofibrosis and all three entities can transform into acute myeloid leukemia.

Polycythemia vera

Diagnostic criteria

Males and females with hematocrit (Hct) > 0.52 and > 0.48 (well above 99th percentile) for more than 2 months should be evaluated. The diagnostic work-up of PV will be reviewed here, for diagnostic work-up of erythrocytosis other than PV please see the 2009 version of the guidelines at www.nmpn.org. A diagnosis of PV should be made using WHO criteria.[4]

Revised WHO 2008 criteria for polycythemia vera (PV)

Major criteria
1. Hemoglobin > 185 g/L in men, >165 g/L in women (11,5/10,2 mmol/l), or haematocrit > 0.52 in men and > 0.48 in women, or other evidence of increased red cell volume*
2. Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation

Minor criteria
1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria.

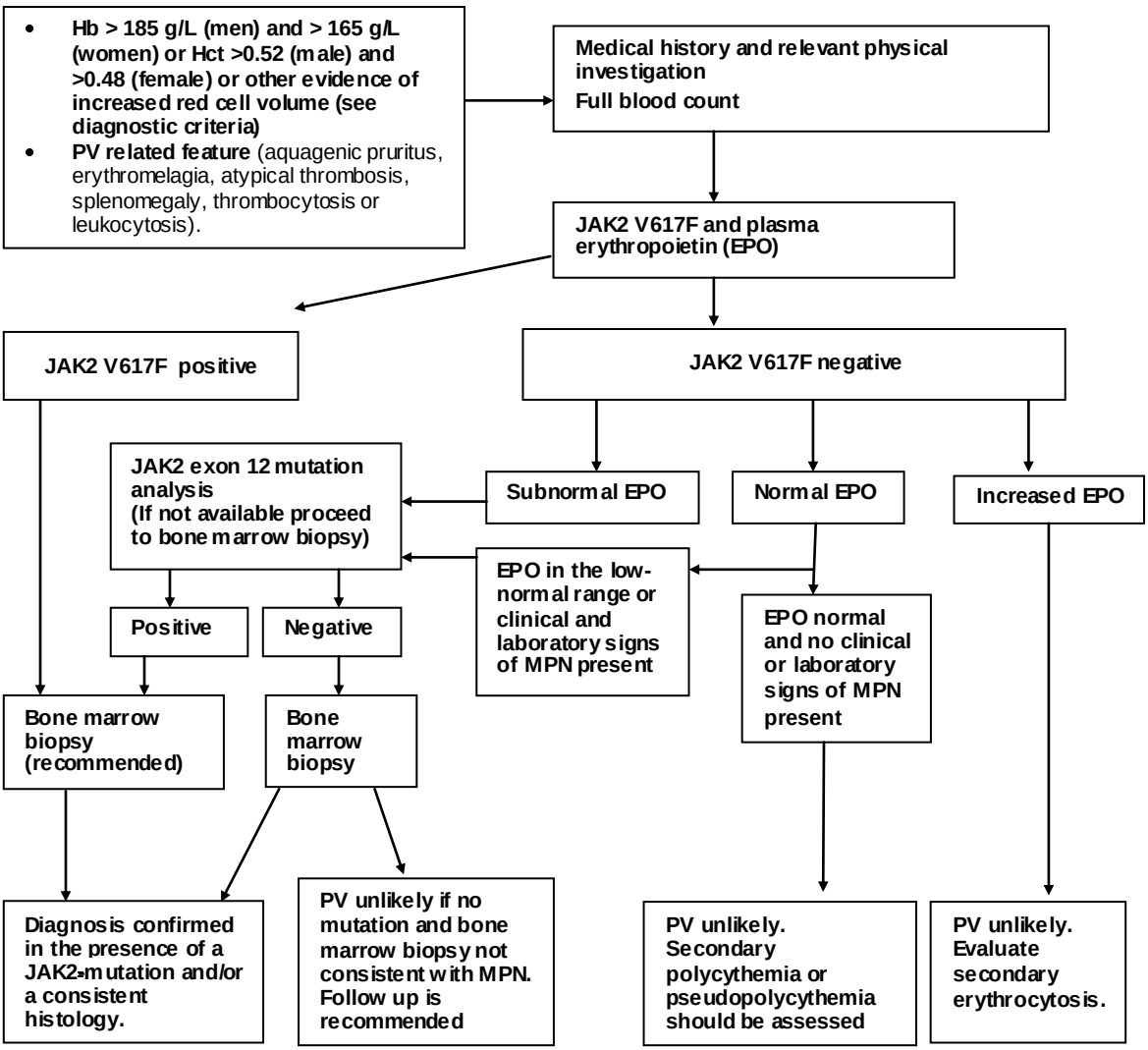
* Hemoglobin or hematocrit greater than 99th percentile of method-specific reference range for age, sex, altitude of residence **or** hemoglobin greater than 170 g/L in men, 150 g/L in women if associated with a documented and sustained increase of at least 20 g/L from an individual's baseline value, **or** elevated red cell mass greater than 25% above mean normal predicted value.

A diagnosis of PV can thus be made without bone marrow biopsy if both major criteria are fulfilled. Biopsy is however highly recommended since degree of fibrosis confers valuable prognostic information.[5] The JAK2 V617F mutation is present in at least 95 % of PV patients,[6-9] in later studies up to 98%.[10] The JAK2 V617F mutation is very seldom found in normal individuals (and if so at very low levels < 1 %), in patients with secondary erythrocytosis, and is rarely found in other hematologic disorders with the exception of MDS

RARS-T.[11] If PV is suspected and the patient is negative for the JAK2 V617F mutation, further investigation with JAK2 exon 12 mutations should be carried out, if this analysis is available.

PV should also be suspected in a patient with a Hct/Hb below the diagnostic threshold if this is combined with a PV-related feature, e.g. an arterial or venous thrombotic event, especially in young patients and/or atypical thrombosis (eg. splanchnic vein thrombosis and Budd-Chiari syndrome), aquagenic pruritus, erythromelalgia or other symptoms of acral ischemia, splenomegaly, leukocytosis, thrombocytosis or microcytosis.
Patients with PV typically have a S-erythropoietin (S-EPO) that is subnormal or in the lower reference interval.

Diagnostic algorithm for polycythemia vera



Diagnostic work-up

- Full blood count with differential count
- Iron status
- ASAT, ALAT, bilirubin, creatinine, uric acid, lactate dehydrogenase (LDH)
- S-erythropoietin
- JAK2 V617F mutation
- JAK2 exon 12 mutation in JAK2 V617F-negative patients, if available
- Bone marrow biopsy
- Physical examination including palpation of spleen
- Evaluation of cardiovascular risk factors

Risk stratification in PV

Polycythemia vera is associated with an excess mortality and reported median survival varies from 10 to 20 years in different studies.[12-14] In order to achieve the clinical goals listed below risk stratification of patients is essential.

High risk

Patients > 60 years or with previous thrombosis or platelets > 1500 x 10^9/l. These patients should be treated with cytoreductive therapy. PV patients with isolated erythrocytosis i.e. normal white cell and platelet counts can initially be treated with phlebotomy alone, until leukocytosis or thrombocytosis occurs.

Low risk

Patients < 60 years, no previous thrombosis and platelets < 1500 x 10^9/l. These patients should in general not receive cytoreductive therapy, but can be considered in certain situations (see below).

Clinical management of polycythemia vera

Goals of therapy in polycythemia vera

- avoid first occurrence and/or recurrence of thrombotic and bleeding complications
- reduce constitutional symptoms (weight loss, night sweats, fever, pruritus)
- manage risk situations (e.g. pregnancy, surgery)
- minimize the risk of acute leukemia and post-PV myelofibrosis

Summarized recommendations

- Vigorous treatment of cardiovascular risk factors
- Phlebotomy to maintain a Hct < 0.45
- Aspirin 75 - 100 mg/day unless contraindicated
- Cytoreduction should be given to high-risk patients. The goal of therapy should be normalization of peripheral blood counts.
- Cytoreduction can also be considered in low risk patients:
    - with poor tolerance/high frequency of phlebotomies
    - with symptomatic or progressive splenomegaly
    - with other evidence of disease progression e.g. weight loss, night sweats
    - with progressive leukocytosis and/or thrombocytosis

- Stem cell transplantation is very seldom performed in PV and should be reserved for the occasional patient that does not respond to conventional cytoreductive therapy

Phlebotomy

The hematocrit should be maintained at less than 0.45 in all patients, as shown in a recent randomized trial.[15] There is currently no evidence to support a different level of Hct in males and females. Hemoglobin levels should not be used for decision-making regarding phlebotomy. **Grade A recommendation, evidence level Ib.** For explanation of grading system – see p. 31.

Aspirin therapy

Aspirin has been shown to reduce both arterial and venous thrombosis in PV[16] and should be given to all PV patients unless it is contraindicated. In Finland, 50mg tablets are available and the recommended dose is 100mg. In the other Nordic countries the recommended dose is 75mg per day. **Grade A recommendation, evidence level Ib**

Aspirin should **not** be given to patients with platelets > 1,500 x 10^9/L due to an increased risk of bleeding, instead cytoreductive therapy should be initiated. In case of aspirin allergy, clopidogrel can be used but no there is so far no data on its efficacy in PV. Trials on clopidogrel in PV are ongoing. The combination of aspirin and anagrelide should in general be used with some caution due to an increased risk of bleeding[17] and is not recommended in patients with previous bleeding.

Choice of cytoreductive therapy in PV

- <60 years: 1st line interferon-α, 2nd line hydroxyurea, 3rd line anagrelide*
- >60 years: 1st line hydroxyurea or interferon-α, 2nd line anagrelide*
- >75 years or with a short expected survival 1st line hydroxyurea, 2nd line *intermittent* busulfan, 3rd line ^{32}P

Combination therapy (hydroxyurea+anagrelide*, hydroxyurea+interferon α) can be an alternative second line therapy in fit patients if dose-limiting side effects occur with monotherapy.

* anagrelide only if the indication for therapy is thrombocytosis

Grade C recommendation, evidence level IV

Interferon-α

Interferon-α (IFN-α) is theoretically superior for treating PV as molecular remissions can be achieved with IFN.[18-21] IFN does not increase the risk of leukemia.[3] It is along with ruxolitinib the most effective drug for PV related pruritus.

Recommendation: IFN or pegylated IFN is the drug of choice in younger patients (<60 years) and is most likely tolerated in these patients. **Grade B recommendation, evidence level III.**

It can also be given to older fit patients and also during pregnancy. Pegylated forms of IFN are at least equally effective as conventional IFN, and seem to cause fewer side effects.

Hydroxyurea

The European Leukemia Network (ELN) recommends Hydroxyurea (HU) or interferon (IFN) as first line therapy in PV patients at any age.[3] Hydroxyurea is the best documented drug in

PV having been the subject of large randomized trials.[22,23] By itself it has very limited leukemogenic potential, if any.[24] However, long-term use of HU in PV has not been able to prevent lekemogenic transformation in 10-20 % of patients after 20 years of therapy in some trials.[25] HU is not recommended during pregnancy, and should be withdrawn at least 3 months before conception both in males and females.

Recommendation: Hydroxyurea is recommended as first-line cytoreductive therapy in PV in patients >60 years or younger patients that do not tolerate IFN**. Grade A recommendation, evidence level Ib.** The documented high leukemia transformation rate despite long term HU treatment (see above),[25] suggests that HU should be limited in patients below 60 years. **Grade C recommendation, evidence level IV.** For dosing and practical recommendations, see page 16.

Anagrelide

Anagrelide is megakaryocyte specific and is therefore only effective in controlling the platelet count, and probably does not control progression of PV.

Recommendation: Anagrelide may be used to control thrombocytosis in PV patients that cannot tolerate or do not respond to IFN or HU, and when HU is considered a less suitable alternative. **Grade C recommendation, evidence level IV.** Due to risk of cardiovascular events, cardiac arrhythmias, and cardiomyopathy, patients should have normal cardiac function. A recent report from Shire states that Anagrelide can give serious adverse cardiac events also in patients with normal cardiac function. The combination of aspirin and anagrelide should in general be used with some caution due to an increased risk of bleeding[17] and is not recommended in patients with previous bleeding. Anagrelide should not be used during pregnancy.

Busulphan

Busulphan (BU) is an alkylating agent and can increase the leukemic transformation rate.
Recommendation: BU should be reserved for patients 75 years or older, or for patients not tolerating HU, IFN or anagrelide. **Grade B recommendation, evidence level III.** Low dose *intermittent* busulfan is more efficacious in controlling PV than radioactive phosphorus.[26] **Grade A recommendation, evidence level Ib.**

Radioactive phosphorus

Radioactive phosphorus (P^{32}) can control elevated blood counts in PV. Infrequent intermittent treatment is required and follow-up can therefore be minimized. It is valuable in older patients if compliance with continuous oral therapy is a problem.

Recommendation: Due to the leukemogenic effect, P^{32} use should be limited to patients older than 75 years where HU, IFN, BU or anagrelide are not suitable.[27] **Grade A recommendation, evidence level Ib**

JAK2 inhibitors

Since no JAK2 inhibitor has been studied extensively in PV to date, these drugs are at the present time experimental and should not be used outside of the context of clinical trials.

Evaluation of response and follow up

The goal of therapy should be normalized peripheral blood counts. Consider changing therapy in patients with resistance or intolerance to ongoing therapy and in patients not achieving treatment goals. The ELN have published criteria for hydroxyurea resistance and intolerance.[28]

Patients on phlebotomy alone should be monitored with complete blood counts at least every 4 to 6 weeks. For recommendations regarding patients on cytoreductive therapy, see p. 17-18.

There is no indication to use repeated bone marrow trephine biopsies for routine follow-up in PV, but is essential in assessing transformation to myelofibrosis or acute leukemia.

Monitoring of molecular response, including sequential assessment of the $JAK2_{V617F}$ allele burden is at the moment not recommended for routine clinical use.

Essential thrombocythemia

All patients with unexplained and persistent thrombocytosis above 450 x10^9/l should be investigated for the possibility of an MPN.
Essential thrombocythemia (ET) is now diagnosed according to the 2008 WHO diagnostic criteria which differ from the former PVSG criteria in that some ET patients with fibrosis would according to the WHO be classified as early myelofibrosis and not as ET,[4] see also page 19). There is however no significant difference in the risk of thrombosis between the two entities,[29] and therefore no reason for not extending the existing clinical care recommendations to also apply to ET classified by WHO. It is of paramount importance that a diagnosis of ET is made using the 2008 WHO criteria, highlighting the absolute need of a bone marrow biopsy in the diagnostic workup of the patient.

Diagnostic criteria

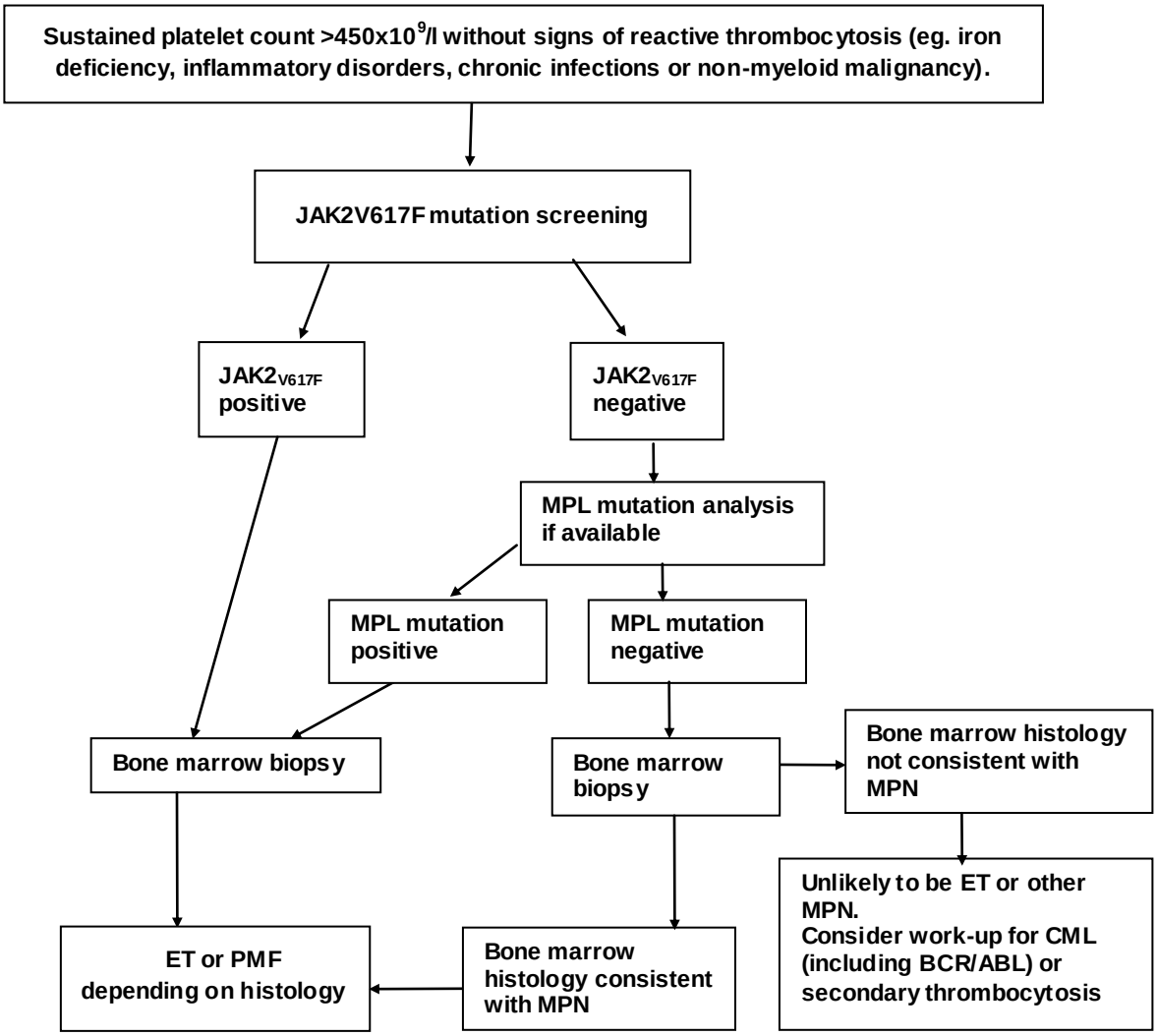
Revised WHO 2008 criteria for essential thrombosis (ET)

1. Sustained platelet count >450x10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes. No significant increase of left-shift of neutrophil granulopoiesis or erythropoiesis.
3. Not meeting WHO criteria for polycythemia vera, primary myelofibrosis, BCR-ABL positive chronic myelogenous leukemia or myelodysplastic syndrome or other myeloid neoplasm.
4. Demonstration of JAK2 V617F or other clonal marker, or in the absence of JAK2 V617F, no evidence for reactive thrombosis.

All four criteria must be met.

Screening for JAK2 V617F mutation should be included in the initial work-up of all patients with suspected ET (positive in 50-60 % of ET patients[6-9]). JAK2 negative patients should be screened for mutations in the thrombopoietin receptor MPL (W515L and W515K), which is positive in around 3% of JAK2 negative ET patients,[30,31] if this analysis is available.
Even in the presence of a mutation in JAK2 or MPL, a diagnosis of ET requires exclusion of PV and PMF. It is important to differentiate ET from prefibrotic/early and overt PMF since there are significant differences in disease progression, leukemic transformation and survival.[29]
In the absence of a clonal marker (JAK2, MPL) it is important to rule out other myeloid malignancies and secondary causes of thrombocytosis such as connective tissue disease, malignant lymphomas, bleeding and iron deficiency.

Diagnostic algorithm in essential thrombocythemia



Diagnostic work-up

- Full blood count with differential count
- Iron status
- ASAT, ALAT, bilirubin, creatinine, uric acid, LDH
- S-erythropoietin
- JAK2 V617F mutation
- MPL mutation in JAK2 negative patients, if available
- Bone marrow biopsy
- BCR-ABL in JAK2 V617-negative patients if differentiation against chronic myelogenous leukemia is not clear
- Evaluation of cardiovascular risk factors
- Physical examination including palpation of spleen

Risk stratification in ET

The risk stratification system in ET is based on the assessment of risk of thrombosis, as the current therapy in ET is aimed at lowering the risk of thrombosis. Extreme thrombocytosis is also included in the risk stratification as it can be associated with acquired von Willebrand disease and bleeding tendency. In the absence of high-risk features, cytoreductive therapy is generally not recommended for patients with cardiovascular risk factors, but could be considered on a case-by-case basis.[32] ET has over the last decades been associated with a normal life expectancy is in most,[14,33] but not all,[12] studies. True ET diagnosed according to the 2008 WHO classification hos not been reported to affect the life expectancy of patients.[29] New prognostic scoring systems have been presented,[34,35] based on additional risk factors such as high leukocyte count and cardiovascular risk factors, but until these are thoroughly validated, recommendations are based on the following risk groups.

High risk

ET patients > 60 years or with a history of previous thrombosis should be treated with cytoreductive therapy in order to prevent thrombosis.

ET patients with a platelet count > 1,500 x 10^9/L should be treated with cytoreductive therapy in order to avoid bleeding.

Low risk

ET patients < 60 years, no previous thrombosis and a platelet count < 1,500 x 10^9/L should normally not be treated with cytoreductive therapy.

Clinical management of essential thrombocythemia

Goals of therapy in essential thrombocythemia

- Prevent first occurrence or recurrence of thrombotic and bleeding complications.
- Minimize the risk of acute leukemia and post-ET myelofibrosis
- Reduce constitutional symptoms (weight loss, night sweats, fever)
- Manage risk situations (e.g. pregnancy and surgery).

Summarized recommendations

- Vigorous treatment of cardiovascular risk factors
- Aspirin 75 - 100 mg/day to selected patients, see below
- Cytoreduction should be given to high-risk patients. The goal of therapy should be normalization of peripheral blood counts.
- Cytoreduction can also be considered in low risk patients with uncontrolled cardiovascular risk factors
- Cytoreduction can also be considered in low risk patients with any of the below mentioned features. It is important to stress that before starting therapy these patients should be evaluated for eventual progression to myelofibrosis:
    - with symptomatic or progressive splenomegaly
    - with other evidence of disease progression e.g. weight loss, night sweats
    - with progressive leukocytosis and/or thrombocytosis
- Stem cell transplantation is almost never performed in ET.

Aspirin

Antiplatelet therapy with aspirin 75 mg per day is recommended, unless otherwise contraindicated, for some ET patients namely

- high risk ET patients
- low risk ET patients with one or more risk factor for cardiovascular disease
- low risk ET patients with microvascular symptoms (erythromelalgia)

Aspirin is generally not recommended in low risk patients with no cardiovascular risk factors, but may be considered in low risk JAK2 positive patients since JAK2 positive patients may have a higher risk of thrombosis[36] and retrospective data indicate a lower thrombotic risk in aspirin-treated JAK2 positive patients.[37]

Patients with a platelet count > 1,500 x 10^9/L should not be treated with aspirin due to increased bleeding risk, instead cytoreductive therapy should be initiated. ASA should be started again when platelets are stable < 1,000 x 10^9/L.

The combination of aspirin and anagrelide should in general be used with some caution due to an increased risk of bleeding,[17] and is not recommended in patients with previous bleeding.

Choice of cytoreductive therapy in ET

- <60 years: 1st line interferon-α, 2nd line hydroxyurea or anagrelide*
- >60 years: 1st line hydroxyurea or interferon-α, 2nd line anagrelide*
- >75 years or with a short expected survival 1st line hydroxyurea, 2nd line *intermittent* busulfan, 3rd line ^{32}P

Combination therapy (hydroxyurea+anagrelide*, hydroxyurea+interferon α) can be an alternative as second line therapy in fit patients if dose-limiting side effects occur with monotherapy.

* anagrelide only if the indication for therapy is thrombocytosis

Grade C recommendation, evidence level IV

Interferon-α

Interferon-α (IFN) treatment is well documented and safe in ET and is not considered leukemogenic or teratogenic.[1] Pegylated IFN given sc weekly has been shown to have equal efficacy as conventional IFN given three times weekly.[38,39] We have a long standing therapy tradition in the Nordic countries using IFN in ET, whereas the ELN does not recommend IFN in ET due to the lack of larger trials in ET.[3]

Recommendation: IFN is the recommended first line therapy in younger patients. It can be used in older patients if long-term use of HU is not suitable and in patients who do not tolerate HU. **Grade B recommendation, evidence level III.** IFN or pegylated IFN is the treatment of choice if cytoreductive therapy is indicated during pregnancy or when pregnancy is planned.

Hydroxyuea

Hydroxyurea (HU) is the best-documented therapy in ET and is recommended as a first-line therapy in the majority of ET patients. HU markedly reduces thrombotic complications compared to aspirin alone.[40] HU was more effective than anagrelide in reducing arterial

thrombotic events in the PT1- trial.[17] HU should not be used during pregnancy or when pregnancy is planned.
Recommendation: Hydroxyurea is recommended as a first-line cytoreductive therapy in ET patients > 60 years of age. **Grade A recommendation, evidence level Ib.**

Anagrelide

Anagrelide is not considered leukemogenic but was associated with a higher risk of bone marrow fibrosis in the PT-1 trial.[17] In the same trial anagrelide was more effective than HU in preventing venous thrombosis. Due to known cardiovascular side effects (palpitations most frequent), anagrelide is only recommended in patients without congestive heart failure or cardiac arrhythmias. Anagrelide should not be used during pregnancy or when pregnancy is planned, since there are no data available concerning effects on the fetus.

Recommendation: Anagrelide can be used in patients where long-term use of IFN or HU is not suitable, and only when platelet reduction is the goal of therapy. Due to risk of cardiovascular events, cardiac arrhythmias, and cardiomyopathy, patients should have normal cardiac function. A recent report from Shire states that Anagrelide can give serious adverse cardiac events also in patients with normal cardiac function. Anagrelide should not be used during pregnancy. **Grade B recommendation, evidence level III.**

Busulphan

Busulphan (BU) is an alkylating agent given as intermittent treatment. BU effectively controls platelet count but is associated with an increased risk of progression to acute leukemia, particularly when used sequentially with hydroxyurea. BU is a second- or third-line agent and should be restricted to patients with short life expectancy.

Recommendation: Intermittent BU treatment can be used in patients 75 years or older, or for patients where HU, IFN or anagrelide are not suitable. **Grade B recommendation, evidence level IIb.**

Radioactive phosphorus

Radioactive phosphorus (P^{32}) is an intermittent treatment effective at controlling platelet count. Few randomized studies have been conducted with P^{32}, in a PVSG trial P^{32} showed comparable effect with melphalan after one year from medication.[41] P^{32} is associated with an increased risk of progression to acute leukemia, particularly when used sequentially with hydroxyurea. P^{32} should be restricted to patients with short life expectancy and can be valuable in older patients if compliance with continuous oral therapy is a problem.

Recommendation: P^{32} treatment can be used in ET patients with short life expectancy where HU, IFN, BU or anagrelide are not suitable. **Grade A recommendation, evidence level Ib.**

JAK2 inhibitors

Since no JAK2 inhibitor has been studied extensively in ET to date, these drugs are at the present time experimental and should not be used outside of the context of clinical trials.

Response monitoring in ET

The goal of therapy should be normalized peripheral blood counts in patients that tolerate therapy. The ELN have published criteria for hydroxyurea resistance and intolerance.[28] Change of therapy should be considered in patients with resistance or intolerance to ongoing

therapy and in patients not achieving goals of treatment. There is currently no absolute evidence for a correlation between platelet levels < 400 and the reduced risk of thrombosis. Therefore, in patients that develop anemia on HU or IFN treatment consider lowering the dose and allowing a higher platelet number in order to avoid anemia.

There is no indication for repeated bone marrow trephine biopsies in routine follow-up in ET, but is essential in assessing transformation to myelofibrosis or acute leukemia. Monitoring of molecular response, including sequential assessment of the $JAK2_{V617F}$ allele burden is at the moment not recommended for clinical use.

Practical considerations regarding cytoreductive therapy in PV and ET

Interferon

Interferon (IFN) suppresses growth of multipotent hematopoietic progenitor cells. Pegylated interferons, which are administered weekly, are today being used in most centers. The starting dose for pegylated interferon alfa-2a (Pegasys®) is 90 μg subcutaneously once weekly. The large majority of patients respond to a dosage of 90 μg once weekly. When the response is stable, controls every 4-8 weeks is sufficient. The starting dose of pegylated interferon alfa-2b (PegIntron®) is 0,5 μg/kg subcutaneously once weekly. Responses are seen within 2-3 months. If cell counts are still high after 3 months, the dose should be increased. Most patients respond to a dose between 0.5 and 0.75 μg/kg. When sufficient effect is reached, taper the dose to the lowest effective dose.

Pegylated interferons can be associated with side effects, e.g. flu-like symptoms and psychiatric disorders. Therefore, interferons are contraindicated in patients with pre-existing psychiatric conditions. Flu-like symptoms may be transient and can be well controlled by paracetamol. Treatment should be stopped if patients develop psychiatric disorders.

Hydroxyurea

Hydroxyurea (HU) is a non-alkylating, non-specific myelosuppressive drug. The recommended starting dose is 500-1000 mg daily (15-20 mg/kg/day). Elderly patients (>70 years old) are usually started on 500 mg/day. In situations when rapid platelet reduction is needed higher starting doses (1500-2000 mg/day) are recommended. Elevated leukocyte and platelet counts may decrease within days. Follow up with full blood count (FBC) is recommended every second week initially. The dose should be adjusted in order to achieve a stable platelet count of 200 – 400 $x10^9$/L. When this is achieved, FBC controls every 4 to 8 weeks is usually sufficient. The average dosage needed is approximately 10-14 tablets a week, lower in elderly patients.

Leukopenia with neutrophil count of 1.0 – 1.5 $x10^9$/L and anemia can occur during the first 3-6 months and is accepted when the goal is to reduce large splenomegaly. In some cases the neutropenia or anemia is dose limiting, but if the platelet count can be kept below 600 $x10^9$/L, this can sometimes be acceptable.

Hydroxyurea should be administered continuously. Interruptions in the treatment can result in abrupt rise in the platelet count and risk of thrombosis.

Some patients will experience other significant side effects from HU, including gastrointestinal disturbance, skin pigmentation, mucocutaneous and leg ulcers. The latter can be seen in up to 10% of patients, and do not heal until HU is discontinued.

Anagrelide

Anagrelide acts on the post-mitotic phase of megakaryocyte development, showing a selective effect on megakaryocytes in vitro. Anagrelide (Xagrid®) capsules contains 0,5 mg and the starting dose is 1 capsule twice daily. FBC should be checked once a week during the first few weeks as the platelet count may fall abruptly. If needed, the dosage can be increased with one capsule (0.5 mg) after 1-2 weeks but the dosage should not be increased with more than one capsule/day per week. The average dosage is 2-2.5 mg daily divided in 2-3 doses to achieve a satisfactory platelet level between 200-400 $x10^9$/l. The maximum dosage should not exceed 10 mg daily, or 3 mg in one single dose. Some patients with troublesome side effects (palpitations or gastrointestinal problems most frequent) may need the daily dosage divided in 3-4 doses.

Due to risk of cardiovascular events, cardiac arrhythmias, and cardiomyopathy, patients should have normal cardiac function. An ECG and an echocardiogram are recommended before Anagrelide is started. A recent report from Shire states that Anagrelide can give serious adverse cardiac events also in patients with normal cardiac function. The combination of aspirin and anagrelide should in general be used with some caution due to an increased risk of bleeding[17] and is not recommended in patients with previous bleeding. When the response is stable, controls every 4-8 weeks is sufficient. Anagrelide should not be used during pregnancy.

Busulphan

Busulphan is an alkylating agent that is given intermittently. Start with 2-4 mg daily until response (normally 2-6 weeks). A full blood cell count should be checked every week while the patient is on busulphan therapy. The leukocyte count may increase during the first 10 to 15 days, this should not be interpreted as resistance to the drug and the dose should not be increased. If busulphan is started at 4 mg/day, the dose should be lowered to 2 mg/d when platelets start to decrease, typically within 2-6 weeks. Busulphan should be stopped when the platelet count reaches 400 $x10^9$ as platelets will continue to fall for another 2-3 weeks. Busulphan can be repeated when the platelet count rises above 400 $x10^9$ again.

Radioactive phosphorus

Radioactive phosphorus (P^{32}) is an orally given radioactive treatment that effectively controls hematopoiesis. P^{32} is associated with an increased risk of progression to acute leukemia, particularly when used sequentially with hydroxyurea. Blood counts should be checked every other week until platelet counts have normalized, after that every 8-12 weeks. The dose of P^{32} is adjusted according to age, weight and previous treatment and is calculated by the radiotherapists.

Primary Myelofibrosis

General introduction

Primary myelofibrosis (PMF) is characterized by progressive accumulation of connective tissue and endothelial proliferation in the bone marrow accompanied by extramedullary hematopoiesis with enlargement of the spleen and liver. PMF is associated with a significant excess mortality and the median survival of PMF patients is 5-6.5 years with a wide range.[12,42,43] Survival of patients with early PMF (see below) has been estimated to be longer than 10 years in a recent study.[44]

Diagnostic criteria

Revised WHO criteria for primary myelofibrosis (PMF)

Major criteria

1. Presence of megakaryocyte proliferation and atypia*, usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for PV, CML, MDS, or other myeloid neoplasm**
3. Demonstration of JAK2617V>F or other clonal marker (e.g., MPL515W>L/K), or in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases***

Minor criteria

1. Leukoerythroblastosis
2. Increase in serum lactate dehydrogenase level****
3. Anemia****|
4. Palpable splenomegaly****

Diagnosis requires meeting all 3 major criteria and 2 minor criteria.

*Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

**Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required. Requires the absence of bcr-abl. Requires the absence of dyserythropoiesis and dysgranulopoiesis.

***Secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met.

****Degree of abnormality could be borderline or marked.

Early "Prefibrotic" Myelofibrosis

The concept of early "prefibrotic" myelofibrosis is increasingly recognized as the early phase of myelofibrosis in the biological continuum from early disease stage to the advanced burnt-out stage of myelofibrosis with myeloid metaplasia. Accordingly, early "prefibrotic" PMF was included in the revised 2008 World Health Organization (WHO) classification.[4] Early PMF is characterized by a hypercellular bone marrow with megakaryocytic, and in contrast to true ET, also granulocytic proliferation. Megakaryocytes show extensive tight clustering and condensed nuclei with clumped chromatin and abnormal nuclear-cytoplasmic ratio. Reticulin fibrosis is absent or minimal.[4] It is important to recognize that early PMF exhibits the three major criteria of the WHO classification shown above, but leukoerytroblastosis, splenomegaly and anemia is most often not present. Although most experienced pathologists acknowledge the diagnosis of early PMF, there is still some controversy around this concept as a separate disease entity and how to distinguish this from ET by distinct histopathological features has not been universally accepted. [45]
In clinical practice the occurrence of anemia, elevated leukocyte count or elevated LDH in "ET" patients should alert the clinician to reevaluate the diagnosis and rule out PMF.[46]

A large retrospective trial of 1104 patients diagnosed as having ET by PVSG criteria were reanalyzed by one of the authors of the WHO 2008 classification. In 891 patients (81 %) the diagnosis was confirmed as ET, whereas 180 patients (16 %) were reclassified as early PMF and 33 patients were not evaluable. Clinical follow-up of these patients showed no differences in thrombosis rates. In contrast, 10 and 15 year overall survival was markedly lower in early PMF, 76 vs. 89 % at 10 years and 59 vs. 80 % at 15 years, respectively. Survival in ET was not different from a sex- and age-standardized European population. Rates of transformation to acute leukemia and progression to overt PMF were clearly increased in early PMF.[29] Further analyses of this cohort has shown that major bleeding was more common in early PMF compared to ET, especially in patients treated with aspirin.[47] Finally, in a substudy where 178 ET patients below 40 years of age at diagnosis were compared to 35 patients with early PMF, progression to overt PMF was more common in patients with early PMF and there was a trend towards more arterial thrombosis.[48] Transformation to leukemia was not observed during a median follow-up of 7.6 years.

There is currently no evidence that treatment of early myelofibrosis is associated with prolonged survival. The majority of patients in the studies above received HU therapy. Whether other treatment modalities such as interferon can prevent or prolong time to overt PMF progression is unknown, but there are ongoing studies to address this question. For the time being patients with early MF without risk factors should not be treated with cytoreductive therapy outside study protocols. In patients with risk factors and an indication for cytoreductive treatment for platelet reduction we recommend the same treatment and treatment goals as for ET (see ET chapter).

Diagnostic work-up of PMF

- Full blood count with differential count
- Iron status
- ASAT, ALAT, bilirubin, creatinine, uric acid, LDH
- S-erythropoietin
- JAK2 V617F mutation
- MPL mutation in JAK2 negative patients, if available
- BCR-ABL in JAK2V617-negative patients if differentiation against chronic myelogenous leukemia is not clear
- Bone marrow biopsy
- Bone marrow cytogenetics (in patients < 60 years to assess prognostic stratification and the indication for SCT)
- Physical examination including palpation of spleen
- Evaluation of cardiovascular risk factors

Prognosis and Risk stratification in PMF

Complications of PMF are common and contribute significantly to morbidity and mortality. Common complications are infections (20-60%) cardiovascular events (20-50 %), thromboembolic (10-40%), and hemorrhagic events (30%). Transformation to acute leukemia is seen in about 10-30 % of the patients.[36,42,49-51]

The $JAK2_{V617F}$ -mutation is positive in 50-60% of PMF-patients[6-9] The prognostic value of the JAK2 mutation have in most studies not been shown to affect survival but a low allele burden has been associated with a poorer prognosis [52] However, this issue is controversial and further studies are required to delineate if JAK2-positive PMF-patients have a clinical phenotype and a prognosis that differ from those who are JAK2-negative.

The previous Lille scoring system has been replaced by the international prognostic scoring system (IPSS) which later has been updated to the dynamic IPSS (DIPSS) and DIPSS plus.

International Prognostic Scoring System (IPSS)

The International prognostic scoring system (IPSS) was introduced by the International Working Group for Myelofibrosis Research and Treatment in 2009.[42] The IPSS is used for risk stratification at diagnosis. Patients are divided into four prognostic groups; low risk, intermediate-1 (Int-1), intermediate-2 (Int-2), and high risk, based on five risk factors, see table. These prognostic scores do not include early (prefibrotic) PMF and neither post-PV nor post-ET MF even though in clinical practice and in studies the two latter are also classified according to these systems.

Dynamic International Prognostic Scoring System (DIPSS) and DIPSS plus

The IPSS has been modified to dynamic IPSS (DIPSS) that can be used at any time during the course of the disease.[51] Recently DIPSS has been upgraded to DIPSS-plus by the incorporation of three additional independent risk factors, see table.[53] The eight DIPSS-plus risk factors define low (no risk factors), intermediate 1 (1 risk factor), intermediate 2 (2-3 risk factors), and high (≥ 4 risk factors) risk groups with median survivals of 15.4, 6.5, 2.9, and 1.3 years, respectively.[53] Leukemic transformation was predicted by the presence of unfavorable

karyotype (complex karyotype or sole or 2 abnormalities including +8, -7/7q-, i(17q), -5/5q-, inv(3), 12p-, or 11q23 rearrangement) or platelet count < 100 x 10^9/L.[53,54]
We recommend the use of IPSS at diagnosis and DIPSS during follow-up. In order to quickly find new adverse prognostic factors, the patient's DIPSS score should be evaluated at every visit. The DIPSS-plus is not yet in clinical use but can be useful in younger patients if there are insecurities regarding risk group and indication for allogeneic stem cell transplantation.

Table 1. Prognostic factors included in the IPSS, DIPSS and DIPSS-plus. For scoring of the DIPSS-plus, see table 3.

Risk factor	IPSS	DIPSS	DIPSS-plus
Age > 65 years	1	1	X
Constitutional symptoms	1	1	X
Hemoglobin < 10g/L	1	2	X
Leukocyte count ≥ 25 × 10(9)/L	1	1	X
Circulating blasts ≥ 1%	1	1	X
Platelet count <100 × 10^9/L			X
Red blood cell transfusion-dependent			X
Unfavorable karyotype			X

Table 2. Risk groups and median survival of the different risk groups in the IPSS and DIPSS.

Risk group	IPSS Number of risk factors	Median survival (months)	DIPSS Number of risk factors	Median survival (months)
Low-risk	0	135	0	Not reached
Intermediate risk-1	1	95	1-2	170.4
Intermediate risk-2	2	48	3-4	48
High-risk	≥3	27	≥4	18

Table 3. Prognostic factors included in the DIPSS-plus and median survival

Risk factor	DIPSS-plus
DIPSS low risk	0
DIPSS int-1 risk	1
DIPSS int-2 risk	2
DIPSS high risk	3
Platelet count <100 × 10^9/L	1
Red blood cell transfusion-dependent	1
Unfavorable karyotype	1

DIPSS plus	Median survival (months)
Low-risk	185
Int-1 risk	78
Int-2 risk	35
High-risk	16

Clinical management of PMF

Patients with post-PV or post-ET MF should be treated according to the guidelines given for PMF below.

Goals of therapy in PMF

- Cure if possible, which means allogeneic stem cell transplantation when indicated
- Treat anemia and other cytopenias when indicated
- Reduce symptomatic splenomegaly
- Reduce constitutional symptoms (weight loss, night sweats, fever, pruritus)
- Avoid first occurrence or recurrence of thrombotic and bleeding complications
- Manage risk situations (e.g. surgery)
- Minimize the risk of acute leukemia

Cure of PMF via stem cell transplantation

Allogeneic stem cell transplant (SCT) is the only curative treatment in PMF, and SCT should be considered in all PMF patients at diagnosis. It is recommended in transplantable patients with Int-2 or high risk at diagnosis, and during follow-up of younger low/Int-1 patients that progress to a higher risk using DIPSS (or DIPSS plus).[3]

Mortality after SCT in PMF is significant and 5-year survival has been between 30% and 60% in different studies.[55-57] Outcome is better for patients with low risk disease, but due to the high toxicity, transplants should only be performed in patients with an expected survival of less than 5 years which includes patients with IPSS, DIPSS, or DIPSS plus risk score of Int-2 or high risk.[55,58-62]

Patients above 45 years have a very poor survival on myeloablative conditioning. Introduction of reduced-intensity conditioning has significantly improved results in the higher age groups but results are still poorer for patients above 60 years of age due to the high transplant-related mortality.[57] Sorror index can be of value in selection of patients.[63,64] Results are similar for sibling donors and matched unrelated donors in the Nordic countries.[57]

Recommendation: Allo-SCT with myeloablative or reduced intensity conditioning is indicated in young (< 40 years of age) Int-2 or high-risk patients with PMF. Reduced intensity transplantation should be considered for patients aged of 40-60 (65) years with Int-2 or high risk at diagnosis or later during the course of the disease. **Grade B recommendation, evidence level III.**

Treatment of Anemia in Primary Myelofibrosis

Anemia in PMF is multifactorial and deficiency of iron, vitamin B12 and folic acid should always be ruled out before considering other therapies. As a general guideline, pharmacological treatment of anemia should be initiated at Hb levels approximately < 110g/L in symptomatic patients and should be considered in asymptomatic patients with Hb levels <100g/L.

Erythropoietin

Recombinant human erythropoietin has been shown to effectively increase the Hb-concentration in 20-60 % of PMF patients in non-randomized studies.[65] The starting dose is 30.000 U once weekly, and may be increased to twice weekly in patients not responding after 6 weeks of therapy. Darbepoietin-alpha administered once a week is equally effective, but more expensive, and the recommended dose is in the range 150-300ug/week. If no response is seen after 8 weeks of full dose EPO therapy should be discontinued. The goal is an Hb-level around 120 g/L in other hematological malignancies and is reasonable also in PMF. A higher Hb-level should be avoided in order to minimize the risk of thrombosis. A plasma erythropoietin below 125 U/L has been clearly associated with a higher probability of response. However, higher S-EPO levels do not preclude patients from responding.[65]

Recommendation: Erythropoietin is recommended as first-line therapy for treatment of anemia in PMF in patients. **Grade B recommendation, evidence level III.**

Danazol

Androgens stimulate bone marrow function and have been shown to improve Hb in about 40% of the patients, in particular in those patients with only moderate splenomegaly and normal cytogenetics. In general, treatment with Danazol is well tolerated with only moderate toxicity.[66] Side effects include a slight increase in liver enzymes and androgenic side effects in female patients. Danazol is administered at a dose of 200mg x 3/day. Monitoring of liver function is recommended regularly (once monthly). Most patients respond within the first 2-3 months but a subgroup of patients have a late response occurring about 6-8(-9) months after starting therapy. A synergistic effect between human recombinant erythropoietin and danazol has been recorded.[67] Danazol is easily available only in Denmark, in other countries only by individual license.

Recommendation: Danazol is, if available, recommended as an alternative first-line therapy in the treatment of anemia in PMF. **Grade B recommendation, evidence level III.**

Glucocorticoids

Treatment with glucocorticoids is indicated in patients with Coombs positive immune hemolysis, but may also be effective in patients with anemia without overt hemolytic activity. In the latter situation, a staring dose of 30 mg prednisolone is recommended. **Grade C recommendation, evidence level IV**

Thalidomide and thalidomide analogues

Thalidomide can increase the Hb-level and decrease spleen size in PMF patients. Low-dose thalidomide (50mg/day) in combination with prednisolone can improve anemia in 20-30% of patients.[68] However, thalidomide is associated with non-hematological toxicity.

Recommendation: Low-dose thalidomide (50mg/day) + prednisolone (1mg/kg for 2 weeks and afterwards tapering to the lowest dose maintaining an adequate Hb-concentration) is recommended for patients not responding to erythropoietin or danazol. In the rare patient harboring del(5q) lenalidomide should be considered. **Grade B recommendation, evidence level III.**

Treatment of symptomatic splenomegaly and constitutional symptoms

Hydroxyurea

The efficacy and safety of hydroxyurea (HU) (0.5 g/2d – 2 g/d) in the treatment of PMF has been reported in several studies.[69-71] Whereas HU lowers elevated leukocyte and platelet counts within days, regression of an enlarged spleen may take several months. In some patients bone marrow fibrosis may regress during treatment with HU, although this finding has not been reproduced in most recent larger studies.[72]

Recommendation: Hydroxyurea is recommended as first-line cytoreductive therapy in older PMF patients not eligible for transplantation. **Grade B recommendation, evidence level III.**

Interferon-α

Several studies have shown that interferon (IFN) may be efficacious in PMF, in particular patients in the hyperproliferative stage of the disease.[73,74] In addition, IFN is not leukemogenic. IFN-α2 treatment may also be associated with regression of bone marrow fibrosis, especially in patients with lower grades of fibrosis.[75] However, in PMF patients with advanced fibrosis treatment with IFN-α is associated with significant side effects and a high degree of discontinuation.

Recommendation: IFN-α is recommended as first-line therapy in patients < 60 years who are not candidates for transplantation. Patients should be in the hyperproliferative phase of the disease and not have extensive fibrosis. **Grade B recommendation, evidence level III.**

Jak2 inhibitors

Several JAK2 inhibitors have been tested but until now, ruxolitinib is the only one approved in the USA and in Europe. Ruxolitinib has been shown to reduce spleen volume by at least 35 % in 40 % of patients with Int-2 or high risk disease.[76,77] Most patients experience very rapid relief in constitutional symptoms within a few days from start of therapy and the reduction of spleen size is usually seen within 2-6 weeks of therapy. Responses have been durable in the course of the two randomized phase III clinical trials, comparing ruxolitinib to placebo[76] or best available therapy.[77] So far there is no clear evidence that ruxolitinib can slow disease progression. However, a survival benefit has been reported in patients on ruxolitinib when compared to patients on placebo or best available therapy.[76,77] In one center occasional patients experienced rebound symptoms on discontinuation and the drug may therefore be tapered during a period of two weeks if discontinuation is not immediately necessary due to severe side effects.[78,79] This rebound phenomenon has not been seen in a larger patient population.[80] Ruxolitinib has not been studied in patients with low and intermediate-1 risk disease and is not recommended for patients in these disease stages.

Recommendation: Ruxolitinib should be considered in patients with high or int-2 risk disease with marked splenomegaly or constitutional symptoms not being controlled by conventional drug therapy such as HU or interferon. **Grade A recommendation, evidence level 1b.**

Ruxolitinib may also be considered in patients in need of fast relief of splenomegaly and symptoms prior to stem cell transplantation. The drug is currently being investigated in this setting in several trials.

Splenectomy

In addition to mechanical discomfort and early satiety, a massively enlarged spleen is associated with portal hypertension and a hyperdynamic portal flow, implying an increased risk of bleeding from the upper gastrointestinal tract. Furthermore, the enlarged spleen contributes to the development of anemia and thrombocytopenia consequent to pooling and sequestration of red blood cells and platelets. All these features of hypersplenism are alleviated by splenectomy with symptomatic improvement in most patients and a rise in Hb-concentration in about half of the patients. Thrombocytopenia is also improved in approximately 50% of patients.[81,82]

Accordingly, the main indications for splenectomy in PMF include, in addition to pronounced mechanical discomfort, are:

- episodes of upper gastrointestinal bleeding secondary to portal hypertension (varices)
- transfusion-dependent anemia

Since the procedure is associated with significant morbidity (25-30%) and mortality (7-10%) conditioning and timing of the patient and expertize of the surgeon are of utmost importance.[81] There is no evidence in the literature to support the contention that splenectomy is followed by an increased risk of leukemic transformation.[83] Splenectomy prior to SCT in patients with huge spleens is a matter of debate.

Recommendation: Splenectomy should be considered in patients with marked splenomegaly associated with repeated upper gastrointestinal bleeding episodes due to portal hypertension and/or cytopenias secondary to hemodilution, splenic pooling and sequestration of blood cells, not responsive to HU, IFN, or ruxolitinib. **Grade B recommendation, evidence level III**

Splenic irradiation

Several reports have documented that irradiation of the spleen may benefit symptomatic patients with huge spleens. However, the risk of ensuing prolonged and severe cytopenias is considerable, probably also due to an effect on circulating progenitor cells. The improvement of symptoms is in most patients but temporary lasting 6-8 months. Irradiation prior to splenectomy is associated with an increased risk of postoperative bleeding.[84] Irradiation should thus be reserved for patients not responsive to conventional therapy and who are not candidates for splenectomy. **Grade B recommendation, evidence level III**

Other less commonly used therapies in PMF

Busulphan

Busulphan (BU) has previously been used extensively in the treatment of PMF. Low dose (2 mg/day) BU is administered in repeated courses of 1-2 months at intervals of 3-6 months. Busulfan is leukemogenic. The sequential use of HU and BU is accompanied by a high risk of leukemic transformation (about 30%).[24,85] Combination therapy with BU and danazol has been reported to be well tolerated and can alleviate constitutional symptoms and increase Hb-levels in selected patients. **Grade B recommendation, evidence level III**

2-Chlorodeoxyadenosine (2-CdA)

2-Chlorodeoxyadenosine (2-CdA) may be useful in symptomatic patients who do not tolerate other cytolytic agents. In particular, 2-CdA may be used in patients with progressive hepatomegaly and symptomatic leukocytosis and thrombocytosis following splenectomy.[86] It is administered at 0.05-0.1 mg/kg for 7 days monthly for up to five treatment cycles. **Grade B recommendation, evidence level III**

Anagrelide

Anagrelide (0,5 mg – 3 mg /d) may be used in PMF-patients with symptomatic thrombocytosis who do not tolerate other cytolytic agents due to side effects or the development of granulocytopenia without adequate control of the platelet count. This agent does not inhibit progression of myelofibrosis or the production of growth factors in PMF or essential thrombocythemia.[87,88] Due to risk of cardiovascular events, cardiac arrhythmias, and cardiomyopathy, patients should have normal cardiac function. A recent report from Shire states that Anagrelide can give serious adverse cardiac events also in patients with normal cardiac function. Anagrelide should not be used during pregnancy. **Grade B recommendation, evidence level III**

Irradiation of lungs and other sites

Irradiation of the lungs (whole-lung external beam radiotherapy in a single fraction of 100 cGy) may induce marked clinical improvement and decrease in pulmonary artery systolic pressure in patients with pulmonary hypertension due to myeloid metaplasia.

Symptomatic extramedullary hematopoiesis, other than the spleen and liver, may be seen in virtually all organs with infiltrates in the skin, peritoneum (ascites), pericardium (congestive heart failure/pericardial tamponade), pleura, lungs (pulmonary hypertension), brain, spinal cord and bone (granulocytic sarcomas). This can be treated with low dose irradiation.

Avoiding thrombotic and bleeding complications

Retrospective analyses indicate that the incidence of thrombotic complications seem similar in PMF and ET.[29,89] No prospective trials of platelet reducing agents or aspirin has been performed in PMF. We and others suggest that clinicians follow the guidelines given for ET regarding thrombosis and bleeding prevention in PMF.

Evaluation of response and follow up

The evaluation of PMF patients should be focused on the major clinical problem(s). Change of therapy should be considered in patients with resistance or intolerance to ongoing therapy and in patients not achieving treatment goals.

Evaluation of full blood count is recommended at least on a weekly basis when new therapies are started that have a potential to lower blood counts, since PMF patients are especially susceptible to marrow suppression. There is no indication for repeated bone marrow trephine biopsies in routine follow-up in PMF, but bone marrow investigation is essential in assessing transformation to acute leukemia. Quantitative $JAK2_{V617F}$ analysis is recommended in the setting of bone marrow transplantation to monitor residual disease. Outside of the SCT setting, monitoring of molecular response is at the moment not recommended for clinical use.

Management of complications in MPNs

Practical suggestions to guide clinical decisions in these settings remain largely empirical. Therefore the recommendations below follow recent experts' consensus recommendations.

Acute thrombotic events and secondary prophylaxis

The risk of thromboembolic events in PV and ET varies in different studies. Risks as high as 50% have been presented while in more recent studies the reported risks reach 30.7% and 13.4% for ET and PV patients, respectively.[90]

Control of the Hct and platelet count should be optimized. In emergency situations, such as acute cerebrovascular complications or severe digital ischemia, acute platelet apheresis or hemodilution/erythrapheresis can be used in order to achieve a rapid reduction in blood counts. Since the effect is brief, cytoreductive therapy with preferably hydroxyurea should be started as soon as possible in patients not already on cytoreductive therapy. Apart from rapidly lowering the Hct and platelet levels, acute thrombotic events should be treated as in non-MPN patients.

In a retrospective study, 235 PV and 259 ET patients were followed after an arterial (n=341) or venous (n=160) thrombotic event. Cytoreductive therapy reduced the incidence of rethrombosis in the entire cohort by 50% due to a marked reduction of arterial events.[91] Significant prevention of rethrombosis was independently achieved in patients with previous venous thrombosis by both oral anticoagulants and antiplatelet drugs. Since no prospective trials exist, it remains unclear whether it is better to give a short course of warfarin or to continue with long-term therapy for secondary prevention of venous thromboembolism.

Retrospective analyses indicate that the incidence of thrombotic complications seem similar in PMF and ET.[29,89]

Myeloproliferative neoplasms represent the commonest systemic cause of splanchnic vein thrombosis, including Budd-Chiari syndrome and portal vein thrombosis.[92] No evidence-based guidelines can be given regarding long-term therapy after splanchnic vein thrombosis, most clinicians tend to favor continued warfarin therapy if possible. Normalization of any abnormal blood counts is also important.

Bleeding

The most important cause of bleeding in ET and PV is acquired von Willebrand´s syndrome (AvWS) associated with high platelet counts (>1,500 x 10^9/L).[93] Therefore, the most important therapeutic intervention to manage acute bleeding in the thrombocythemic patient is platelet reduction, and the recommended agent is hydroxyurea. Platelet apheresis is indicated when extreme thrombocytosis is accompanied by an urgent need to reduce platelet counts i.e. severe or life-threatening bleeding.[94]

In case of major bleeding, all use of aspirin or anticoagulants should be stopped at once. These drugs should also be avoided in patients with previous bleeding episodes and AvWS.[95] In view of reports of thrombotic complications among non-hematological patients at high risk for thrombosis treated with desmopressin, this agent is not recommended.[96] The same goes for von Willebrand factor-containing plasma products.[97]

The combination of aspirin and anagrelide was in the PT-1 trial associated with an increased risk of bleeding; this combination should therefore be used with caution.[17,95]

Patients with PMF are at higher risk of bleeding than patients with ET.[47] No prospective trial of platelet reducing agents or aspirin has been performed in PMF. We and others suggest that clinicians follow the guidelines given for ET regarding prevention and treatment of thrombosis and bleeding in PMF.

Pruritus

Pruritus, typically aquagenic, can be a severe clinical problem in PV. Antihistamines may be of benefit. Several studies describe improvements with treatment with IFN. Selective serotonin re-uptake inhibitors can also lead to improvement of pruritus. Benefit has been shown with phototherapy using psoralen and ultraviolet A light. Ruxolitinib has been reported to have a good effect on pruritus,[76,77] and should be considered in patients with severe pruritus.

Elective surgical interventions

Patients with MPNs have both a high risk of thrombosis and a high risk of bleeding when undergoing surgery.[95] It is generally recommended to use cytoreductive agents in order to normalize blood counts before elective surgery, but this recommendation is not based on solid data from well-controlled studies. It has been shown that perioperative complications after splenectomy have decreased after prompt use of cytoreductive agents to counteract postsplenectomy thrombocytosis, implying the benefit of lowering elevated blood counts before invasive surgery. Aspirin should be withheld for at least one week before elective surgery. Patients should be monitored closely after major surgery regarding thrombotic complications, especially in the abdominal veins after splenectomy.[95]

Transformation to AML

The results after conventional AML induction chemotherapy are dismal in patients developing AML after PV, ET or PMF, with a very short median survival.[24] Results are not significantly better than palliative therapy. If possible it is recommended that patients undergo allogeneic stem cell transplantation after induction chemotherapy or therapy with azacytidine. Such patients should be discussed with the transplant team in order to choose a proper induction therapy. As a rule, patients with highly proliferative leukemia will need conventional chemotherapy, whereas those characterized by cytopenia may be transplanted upfront or after induction therapy with azacytidine. In patients not eligible for transplantation, a phase II trial of azacytidine suggests that azacytidine may confer a better survival compared to conventional induction.[98]

Pregnancy

There is only limited information in the medical literature about the management of MPNs in pregnancy.[99] The live birth rate is about 60% due to an overall incidence of first trimester miscarriage of 31-36% (about twice that expected) and an increased risk of intrauterine growth retardation, intrauterine death and stillbirth (8%). Major maternal complications are more uncommon and occur in approximately 8% of ET patients.[95,100]

Pregnant MPN patients should be followed in hematology centers with experience in handling pregnancies and in close collaboration with an obstetrical department. Therapeutic strategies for PV and ET in pregnancy are influenced by the patients' disease status and prior obstetric history. If any of the following factors are present, the pregnancy is likely to be at a high risk of complication for the mother and/or fetus:[95]

- Previous venous or arterial thrombosis in mother
- previous hemorrhage attributed to PV/ET
- previous pregnancy complication that may have been caused by PV/ET
    - significant ante- or postpartum hemorrhage
    - severe preeclampsia
    - unexplained recurrent first trimester loss (≥3)
    - intrauterine growth retardation (>5 percentile for gestation)
    - intrauterine death or stillbirth (no other cause identified)
    - placental abruption
- platelet count rising to >1,000x10^9/l

Therapeutic options include antithrombotic treatment, phlebotomy in PV and cytoreductive agents. The optimal Hct in pregnancy has yet to be established but the current recommendation is to maintain the Hct within the normal range appropriate for gestation. The increased plasma volume often results in a reduced Hct and platelet count during the second trimester. The levels rise again during the post-partum period contributing to an increased thrombotic risk during the first six weeks after delivery. Close monitoring of blood counts is important during this period.[100]

Low dose aspirin is safe and seems advantageous during pregnancy in ET. We recommend that in the absence of clear contraindications all PV and ET patients should be on aspirin 75mg per day throughout the pregnancy. In planned pregnancies, aspirin should be started before conception to facilitate formation of placental circulation.[95] Starting on the day of the delivery, aspirin is substituted by a prophylactic dose of low molecular weight heparin (LMWH) which is given until six weeks after delivery.[100] Blood counts should be checked weekly to detect rebound thrombocythemia or polycythemia.

If the mother or fetus is at high risk for complication (see risk stratification), the use of LMWH is indicated during the whole pregnancy and six weeks after delivery. The doses of LMWH that have been reported are dalteparin 5000 U or enoxaparin 40mg daily.

To avoid teratogenic effects, hydroxyurea or anagrelide should be gradually withdrawn 3-6 months prior to conception, also in fathers to be, and may be substituted with IFN if necessary.

Cytoreductive therapy is recommended when the pregnancy is classified as high risk according to the criteria above, when platelet level is >1,000-1,500 x10^9/l or when familial thrombophilia or cardiovascular factors are present. The drug of choice is IFN[101] and pegylated forms of IFN are also considered to be safe.

Breast-feeding is safe with heparin, but contra-indicated with the cytoreductive agents including interferon.

Pediatric MPN

The incidence of different MPN in patients aged less than 20 years is so low that formal evidence based recommendations is impossible to give. This has recently been emphasized by the ELN.[3]

PV and PMF is more uncommon than ET, which in turn is 90-fold less frequent than in adults with an estimated annual incidence of 4 new ET cases per 10 million inhabitants. In children with ET a lower proportion of less than 1 in 3 JAK2 V617F mutated patients has been found. The importance of bone marrow histology in the diagnosis of childhood ET is also undefined at the present,[102] suggesting the need for improved and more specific criteria in childhood ET. In contrast, the WHO criteria for adult PV and PMF can be used in children.[103]

ELN recommends that cytoreductive therapy in children with PV and ET should be given as a last possibility. Therapy in children with PV and ET should be tailored according to the risk profile of the patient.[103,104] High risk in children is arbitrarily defined as previous life threatening major thrombotic or severe hemorrhagic complication. In such children therapy with interferon or HU is recommended as first line therapy by the ELN. In the Nordic region we are concerned with potential long-term leukemogenicity of HU and therefore recommend interferon as first-line therapy in PV. In ET anagrelide can be an alternative to interferon as first-line therapy.

Low risk PV patients are recommended to be treated with phlebotomy to maintain a hematocrit < 0.45. Aspirin is warranted if they have microcirculatory symptoms or concomitant cardiovascular risk factors. Aspirin may also be given to patients without such problems based on the ECLAP study in adults,[16] but no formal studies have been performed of it´s efficacy in children.

Low risk ET patients are given aspirin if they have microcirculatory symptoms or concomitant cardiovascular risk factors. In asymptomatic pediatric patients aspirin should be used with caution due to the risk of Reye's syndrome.[104]

The natural course of PMF seems different from that in adults. Variable outcomes with either a fulminant course rapidly evolving to acute leukemia or on the other hand a relatively indolent course have been described. It is imperative that children with PMF are evaluated for stem cell transplant using the same risk score as in adults. Other palliative treatments also follow the recommendations given for adults.

Evidence levels and recommendations grades

Where possible and appropriate, recommendation grade (A, B and C) and evidence level (I-IV) are given (for definitions see Table 1). Grade A does not imply that a treatment is more recommendable than a grade B, but implies that the given recommendation regarding the use of a specific treatment is based on at least one randomized trial.

Table 4.
A) Levels of evidence

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomized trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports and/or clinical experiences of respected authorities

B) Grades of recommendation

Grade	Evidence level	Recommendation
A	Ia, Ib	Required: At least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required: Availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C	IV	Required: Evidence obtained from expert committee reports or opinions and /or clinical experiences of respected authorities. Indicates absence of directly applicable studies of good quality

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